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**Computational Intelligence Lab**

# Master's Thesis:

# Using Machine Learning Techniques to Improve the Behavior of a Medical Decision Support System

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# Chapter1:

# Health informatics

## 1.1 DEFINITION

**Health informatics** (also called **health care informatics**, **healthcare informatics**, **medical informatics** or **biomedical informatics**) is a discipline at the intersection of information science, computer science, and health care. It deals with the resources, devices, and methods required to optimize the acquisition, storage, retrieval, and use of information in health and biomedicine. Health informatics tools include not only computers but also clinical guidelines, formal medical terminologies, and information and communication systems. It is applied to the areas of nursing, clinical care, dentistry, pharmacy, public health and (bio)medical research.

### 1.2 History

Medical informatics began to take off in the US in the 1950s with the rise of computers.

Early names for medical informatics included medical computing, medical computer science, computer medicine, medical electronic data processing, medical automatic data processing, medical information processing, medical information science, medical software engineering, and medical computer technology.

Since the 1970s the coordinating body has been the International Medical Informatics Association (IMIA)

### 1.3 Medical informatics in the United States

The earliest use of computation for medicine was for dental projects in the 1950s at the United States National Bureau of Standards by Robert Ledley.[3]

The next step in the mid 1950s were the development of expert systems such as MYCIN and INTERNIST-I. In 1965, the National Library of Medicine started to use MEDLINE and MEDLARS. At this time, Neil Pappalardo, Curtis Marble, and Robert Greenes developed MUMPS (Massachusetts General Hospital Utility Multi-Programming System) in Octo Barnett's Laboratory of Computer Science [4] at Massachusetts General Hospital in Boston.[5] In the 1970s and 1980s it was the most commonly used programming language for clinical applications. The MUMPS operating system was used to support MUMPS language specifications. As of 2004, a descendent of this system is being used in the United States

Veterans Affairs hospital system. The VA has the largest enterprise-wide health information system that includes an electronic medical record, known as the Veterans Health Information Systems and Technology Architecture (VistA). A graphical user interface known as the Computerized Patient Record System (CPRS) allows health care providers to review and update a patient's electronic medical record at any of the VA's over 1,000 health care facilities.

In the 1970s a growing number of commercial vendors began to market practice management and electronic medical records systems. Although many products exist, only a small number of health practitioners use fully featured electronic health care records systems.

Homer R. Warner, one of the fathers of medical informatics,[6] founded the Department of Medical Informatics at the University of Utah in 1968, and the American Medical Informatics Association (AMIA) has an award named after him on application of informatics to medicine.

### 1.3 EUROPE

The European Union's Member States are committed to sharing their best practices and experiences to create a European eHealth Area, thereby improving access to and quality health care at the same time as stimulating growth in a promising new industrial sector. The European eHealth Action Plan plays a fundamental role in the European Union's strategy. Work on this initiative involves a collaborative approach among several parts of the Commission services.[10][11] The European Institute for Health Records is involved in the promotion of high quality electronic health record systems in the European Union.[12]

The NHS in England has contracted out to several vendors for a National Medical Informatics system 'NPFIT' that divides the country into five regions and is to be united by a central electronic medical record system nicknamed "the spine".[13] The project, in 2010, is seriously behind schedule and its scope and design are being revised in real time. The degree of computerisation in NHS secondary was quite high before NPfIT and that programme has had the unfortunate effect of largely stalling further development of the installed base.

Almost all general practices in England and Wales are computerised and patients have relatively extensive computerised primary care clinical records. Computerisation is the

responsibility of individual practices and there is no single, standardised GP system. Interoperation between primary and secondary care systems is rather primitive.

Scotland has an approach to central connection under way which is more advanced than the English one in some ways. Scotland has the GPASS system whose source code is owned by the State, and controlled and developed by NHS Scotland. It has been provided free to all GPs in Scotland but has developed poorly.[*citation needed*] Discussion of open sourcing it as a remedy is occurring.

The European Commission's preference, as exemplified in the 5th Framework[14] as well as currently pursued pilot projects,[15] is for Free/Libre and Open Source Software (FLOSS) for healthcare.

### 1.4 Health informatics law

Health informatics law deals with evolving and sometimes complex legal principles as they apply to information technology in health-related fields. It addresses the privacy, ethical and operational issues that invariably arise when electronic tools, information and media are used in health care delivery. Health Informatics Law also applies to all matters that involve information technology, health care and the interaction of information. It deals with the circumstances under which data and records are shared with other fields or areas that support and enhance patient care.

### 1.5 Clinical Informatics

Clinical Informatics is concerned with use information in health care by clinicians.[29][30]

Clinical informaticians transform health care by analyzing, designing, implementing, and evaluating information and communication systems that enhance individual and population health outcomes, improve [patient] care, and strengthen the clinician-patient relationship. Clinical informaticians use their knowledge of patient care combined with their understanding of informatics concepts, methods, and health informatics tools to:

- assess information and knowledge needs of health care professionals and patients,
- characterize, evaluate, and refine clinical processes,
- develop, implement, and refine clinical decision support systems, and

- lead or participate in the procurement, customization, development, implementation, management, evaluation, and continuous improvement of clinical information systems.

Physicians who are board-certified in clinical informatics collaborate with other health care and information technology professionals to develop health informatics tools which promote patient care that is safe, efficient, effective, timely, patient-centered, and equitable.

### 1.6 mHealth

**mHealth** (also written as **m-health** or **mobile health**) is a term used for the practice of medical and public health, supported by mobile devices. The term is most commonly used in reference to using mobile communication devices, such as mobile phones and PDAs, for health services and information. The mHealth field has emerged as a sub-segment of eHealth, the use of information and communication technology (ICT), such as computers, mobile phones, communications satellite, patient monitors, etc., for health services and information.[1] mHealth applications include the use of mobile devices in collecting community and clinical health data, delivery of healthcare information to practitioners, researchers, and patients, real-time monitoring of patient vital signs, and direct provision of care (via mobile telemedicine).[2]

While mHealth certainly has application for industrialized nations, the field has emerged in recent years as largely an application for developing countries, stemming from the rapid rise of mobile phone penetration in low-income nations. The field, then, largely emerges as a means of providing greater access to larger segments of a population in developing countries, as well as improving the capacity of health systems in such countries to provide quality healthcare.

Within the mHeath space, projects operate with a variety of objectives, including increased access to healthcare and health-related information (particularly for hard-to-reach populations); improved ability to diagnose and track diseases; timelier, more actionable public health information; and expanded access to ongoing medical education and training for health workers

**Definitions**

And multimedia technologies as they are integrated within increasingly mobile and wireless health care delivery systems. The field broadly encompasses the use of mobile telecommunication and multimedia technologies in health care delivery.

While straightforward, the most widely cited definition is by Istepanian et al. as 'emerging mobile communications and network technologies for healthcare' [3]. The 2010 mHealth Summit [1] of the Foundation for the National Institutes of Health (FNIH)[2], uses a slightly varied definitions: that is, "the delivery of healthcare services via mobile communication devices" [4].

While there are some projects that are considered solely within the field of mHealth, the linkage between mHealth and eHealth is unquestionable. For example, an mHealth project that uses mobile phones to access data on HIV/AIDS rates would required an eHealth system in order to manage, store, and assess the data. Thus, eHealth projects many times operate as the backbone of mHealth projects.[1]

In a similar vein, while not clearly bifurcated by such a definition, eHealth can largely be viewed as technology that supports the functions and delivery of healthcare, while mHealth rests largely on providing healthcare access [4]. Because mHealth is by definition based on mobile technology, healthcare, through information and delivery, can better reach areas, people, and/or healthcare practitioners with previously limited exposure to certain aspects of healthcare.

**Motivation of mHealth**

The motivation behind the development of the mHealth field arises from two factors. The first factor concerns the myriad constraints felt by healthcare systems of Developing nations. These constraints include high population growth, a high burden of disease prevalence[5], low health care workforce, large numbers of rural inhabitants, and limited financial resources to support healthcare infrastructure and health information systems. The second factor is the recent rapid rise in mobile phone penetration in developing countries to large segments of the healthcare workforce, as well as the population of a country as a whole [6]. With greater access to mobile phones to all segments of a country, including rural areas, the potential of lowering information and transaction costs in order to deliver healthcare improves.

The combination of these two factors have motivated much discussion of how greater access to mobile phone technology can be leveraged to mitigate the numerous pressures faced by developing countries' healthcare systems. Both factors are discussed here.

**Healthcare in Low- and Middle-income Countries**

(figer1)Disability-adjusted life year for all causes per 100,000 inhabitants in 2004.[7]

no data less than 9250 9250-16000 16000-22750 22750-29500 29500-36250 36250-43000 43000-49750 49750-56500 56500-63250 63250-70000 70000-80000 more than 80000

Middle income and especially low-income countries face a plethora of constraints in their healthcare systems. These countries face a severe lack of human and physical resources, as well as some of the largest burdens of disease, extreme poverty, and large population growth rates. Additionally, healthcare access to all reaches of society is generally low in these countries.

The WHO notes an extreme deficit within the global healthcare workforce. The WHO notes critical healthcare workforce shortages in 57 countries—most of which are characterized as

developing countries—and a global deficit of 2.4 million doctors, nurses, and midwives [8]. The WHO, in a study of the healthcare workforce in 12 countries of Africa, finds an average density of physicians, nurses and midwives per 1000 population of 0.64 [9]. The density of the same metric is four times as high in the United States, at 2.6 [10].

The burden of disease is additionally much higher in low- and middle-income countries than high-income countries. The burden of disease, measured in disability-adjusted life year (DALY), which can be thought of as a measurement of the gap between current health status and an ideal situation where everyone lives into old age, free of disease and disability, is about five times higher in Africa than in high-income countries [11]. In addition, low- and middle-income countries are forced to face the burdens of both extreme poverty and the growing incidence of chronic diseases, such as diabetes and heart disease, an effect of new-found (relative) affluence.[1]

Considering poor infrastructure and low human resources, the WHO notes that the healthcare workforce in sub-Saharan Africa would need to be scaled up by as much as 140% to attain international health development targets such as those in the Millennium Declaration [12].

The WHO, in reference to the healtcare condition in sub-saharan Africa, states:

"The problem is so serious that in many instances there is simply not enough human capacity even to absorb, deploy and efficiently use the substantial additional funds that are considered necessary to improve health in these countries." [12]

**Linking Health and Development**

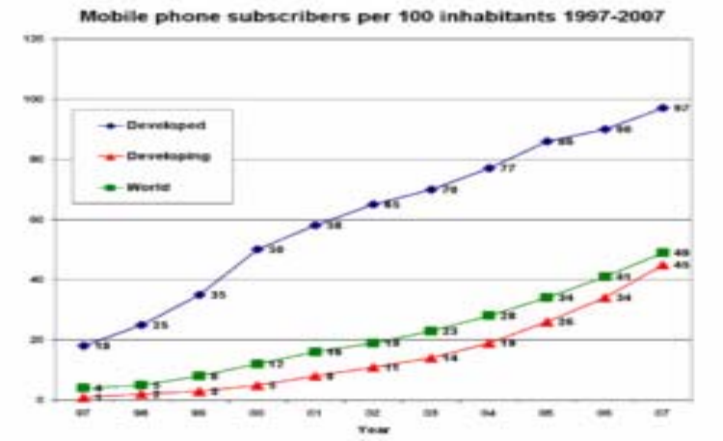
The link between health and development can be found in three of the Millennium Development Goals (MDGs), as set forth by the United Nations Millennium Declaration in 2000. The MDGs that specifically address health include reducing child mortality; improving maternal health; combating HIV and AIDS, malaria, and other diseases; and increasing access to safe drinking water [13]. A progress report published in 2006 indicates that childhood immunization and deliveries by skilled birth attendants are on the rise, while many regions continue to struggle to achieve reductions in the prevalence of the diseases of poverty including malaria, HIV and AIDS and tuberculosis (TB)[14].

### 1.7 Mobile Technology in Low- and Middle-income Countries

Mobile technology has made a recent and rapid appearance into low- and middle-income nations [15]. While, in the mHealth field, mobile technology usually refers to mobile phone technology, the entrance of other technologies into these nations to facilitate healthcare are also discussed here.

**Mobile Phones**

### *1.8 Penetration and Drivers of Growth*




Mobile phone subscribers per 100 inhabitants 1997–2007

Mobile phones have made a recent and rapid entrance into many parts of the low- and middle-income world, with the global Mobile phone penetration rate drastically increasing over the last decade. Improvements in telecommunications technology infrastructure, reduced costs of mobile handsets, and a general increase in non-food expenditure have influenced this trend. Low- and middle-income countries are utilizing mobile phones as "leapfrog technology" (see leapfrogging). That is, mobile phones have allowed many developing countries, even those with relatively poor infrastructure, to bypass 20th century fixed-line technology and jump to modern mobile technology [16].

The number of global mobile phone subscribers in 2007 was estimated at 3.1 billion of an estimated global population of 6.6 billion (47%)[17]. These figures are expected to grow to 4.5 billion by 2012, or a 64.7% mobile penetration rate. The greatest growth is expected in Asia, the Middle East, and Africa. In many countries, the number of mobile phone subscribers has

by-passed the number of fixed-line telephones, this is particularly true in developing countries[18]. Globally, there were 4.1 billion mobile phones in use in December 2008 . See List of countries by number of mobile phones in use.

While mobile phone penetration rates are on the rise, globally, the growth within countries is not generally evenly distributed. In India, for example, while mobile penetration rates have increased markedly, by far the greatest growth rates are found in urban areas. Mobile penetration, in September 2008, was 66% in urban areas, while only 9.4% in rural areas. The all India average was 28.2% at the same time [19]. So, while mobile phones may have the potential to provide greater healthcare access to a larger portion of a population, there are certainly within-country equity issues to consider.

Mobile phones are spreading because the cost of mobile technology deployment is dropping and people are, on average, getting wealthier in low- and middle-income nations [20]. Vendors, such as Nokia, are developing cheaper infrastructure technologies (CDMA) and cheaper phones (sub $50–100, such as Sun's Java phone). Non-food consumption expenditure is increasing in many parts of the developing world, as disposable income rises, causing a rapid increase spending on new technology, such as mobile phones. In India, for example, consumers have become and continue to become wealthier. Consumers are shifting their expenditure from necessity to discretionary. For example, on average, 56% of Indian consumers' consumption went towards food in 1995, compared to 42% in 2005. The number is expected to drop to 34% by 2015. That being said, although total share of consumption has declined, total consumption of food and beverages increased 82% from 1985 to 2005, while per-capita consumption of food and beverages increased 24%. Indian consumers are getting wealthier and they are spending more and more, with a greater ability to spend on new technologies [21].

### 1.9 Technology

Basic SMS functions and real-time voice communication serve as the backbone and the current most common use of mobile phone technology. The broad range of potential benefits to the health sector that the simple functions of mobile phones can provide should not be understated [22].

The appeal of mobile communication technologies is that they enable communication in motion, allowing individuals to contact each other irrespective of time and place [23][24]. This is particularly beneficial for work in remote areas where the mobile phone, and now

increasingly wireless infrastructure, is able to reach more people, faster. As a result of such technological advances, the capacity for improved access to information and two-way communication becomes more available at the point of need.

More advanced mobile phone technologies are enabling the potential for further healthcare delivery. Smartphone technologies are now in the hands of a large number of physicians and other healthcare workers in low- and middle-income countries. Although far from ubiquitous, the spread of Smartphone technologies opens up doors for mHealth projects such as technology-based diagnosis support, remote diagnostics and telemedicine, web browsing, GPS navigation, access to web-based patient information, and decentralized health management information systems (HMIS).

While uptake of Smartphone technology by the medical field has grown in low- and middle-income countries, it is worth noting that the capabilities of mobile phones in low- and middle-income countries has not reached the sophistication of those in high-income countries. The infrastructure that enables web browsing, GPS navigation, and email through Smartphones is not as well developed in much of the low- and middle-income countries[25]. Increased availability and efficiency in both voice and data-transfer systems in addition to rapid deployment of wireless infrastructure will likely accelerate the deployment of mobile-enabled health systems and services throughout the world.[26].

**Other mHealth Technologies**

Beyond mobile phones wireless-enabled laptops and specialized health-related software applications are currently being developed, tested, and marketed for use in the mHealth field. Many of these technologies, while having some application to low- and middel-income nations, are developing primarily in high-income countries. However, with broad advocacy campaigns for free and open source software (FOSS), applications are beginning to be tailored for and make inroads in low- and middle-income countries.

Some other mHealth technologies include

- Patient monitoring devices
- Mobile telemedicine/telecare devices
- MP3 players for mLearning
- Laptop compuers
- Microcomputers
- Data collection software

Data has become an especially important aspect of mHealth. Data collection requires both the collection device (mobile phones, computer, or portable device) and the software the houses the information. Data is primarily focused on visualizing static text but can also extend to interactive decision support algorithms, other visual image information, and also communication capabilities through the integration of e-mail and SMS features. Integrating use of GIS and GPS with mobile technologies adds a geographical mapping component that is able to "tag" voice and data communication to a particular location or series of locations. These combined capabilities have been used for emergency health services as well as for disease surveillance, health facilities and services mapping, and other health-related data collection.

### 1.10 mHealth and Health Outcomes

The mHealth field operates on the premise that technology integration within the health sector has the great potential to promote healthy lifestyles, improve decision-making by health professionals (and patients) and enhance healthcare quality by improving access to medical and health information and facilitating instantaneous communication in places where this was not previously possible [27][28]. It follows that the increased use of technology can help reduce health care costs by improving efficiencies in the health care system and promoting prevention through behavior change communication (BCC). The mHealth field also houses the idea that there exists a powerful potential to advance clinical care and public health services by facilitating health professional practice and communication and reducing health disparities through the use of mobile technology.

Efforts are ongoing to explore how a broad range of technologies, and most recently mHealth technologies, can improve such health outcomes as well as generate cost savings within the health systems of low- and middle-income countries. In some ways, the potential of mHealth lies in its ability to offer opportunities for direct voice communication (of particular value in areas of poor literacy rates and limited local language-enable phones) and information transfer capabilities that previous technologies did not have. Overall, mobile communication technologies are tools that can be leveraged to support existing workflows within the health sector and between the health sector and the general public[29].

Within the mHealth space, projects operate with a variety of objectives, as stated by the UN Foundation and Vodafone Foundation's report on *mHealth for Development*:

- increased access to healthcare and health-related information (particularly for hard-to-reach populations)
- improved ability to diagnose and track diseases
- timelier, more actionable public health information
- expanded access to ongoing medical education and training for health workers [1]

### 1.11 Applications in the mHealth Field

While others exist, the UN Foundation and Vodafone Foundation [1] report presents six application categories within the mHealth field.

- Education and awareness
- Helpline
- Diagnostic and treatment support
- Communication and training for healthcare workers
- Disease and epidemic outbreak tracking
- Remote monitoring
- Remote data collection

Each application category as well as specific project within the category will be described.

### 1.12 Education and awareness

Education and awareness programs within the mHealth field are largely about the spreading of mass information from source to recipient through short message services (SMS). In education and awareness applications, SMS messages are sent directly to users' phones to offer information about various subjects, including testing and treatment methods, availability of health services, and disease management. SMSs provide an advantage of being relatively unobtrusive, offering patients confidentiality in environments where disease (especially HIV/AIDS) is often taboo. Additionally, SMSs provide an avenue to reach far-reaching areas—such as rural areas—which may have limited access to public health information and education, health clinics, and a deficit of healthcare workers [1]

## Below is a list of mHealth Education and Awareness projects:

| Country | Name | Inception | Program size | Major services | Insights and Outcomes | Sponsors | Charges | Telcom partner role |
|---|---|---|---|---|---|---|---|---|
| Mexico | Vidanet | | | Vidanet gives People Living With HIV (PLWHIV) the ability to register to receive messages to help improve their adherence to their specific treatment. The main objective of this Project for ICS is to develop a strategic model of educational communication by promoting projects involving a telecommunication revolution in favor of health. With these tools they can generate changes in attitude towards a self-health care, health risk prevention, and adherence to specific prescribed treatments assigned to PLWHIV. | | Voxiva has partnered with the Instituto Carso de la Salud (ICS) | | |
| Mexico | Cardionet | | | Voxiva, along with ICS, has developed CardioNet, a solution in self-health care, health risk prevention, and adherence to prescribed treatments. Individuals complete a questionnaire asking them questions such as sex, age, weight, height, other health problems they have (i.e. diabetes or smoking) as well as blood pressure and cholesterol if known. Based on these answers, the individual is evaluated according to the standards set by the World Health Organization (WHO). From this assessment the individual begins receiving educational | | Voxiva has partnered with the Instituto Carso de la Salud (ICS) | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | messages encouraging him/her to exercise and eat healthy. Examples of health foods and exercise are given to increase the messages effectiveness. | | | | |
| Rwanda/Uganda | ResultsSMS.org | | | ResultsSMS is an open-source platform compatible with OpenMRS designed to disseminate test results, patient education, follow-up appointments and adherence reminders to patients via SMS. | | ResultsSMS is a partnership between GPAS, FrontlineSMS and Support for International Change with seed funding from the Harvard Initiative for Global Health | | |
| India | Freedom HIV/AIDS | 2005 | In the first phase, ZMQ launched four games on Reliance Infocomm - one of the largest mobile operators of India and was able to reach out to over 9 million handsets. Later, the games were made available on other mobile carriers taking to 30 million handsets. In a span of 15 months, there have been a download of 10,3 million game sessions | Freedom HIV/AIDS comprises four mobile games targeting different mindsets and psychology of mobile users. The games are deployed on low-end black/white to sophisticated high-end colored devices. | | Freedom HIV/AIDS is a social initiative of ZMQ Software Systems. The initiative is supported by Delhi State AIDS Control Society and was launched by Chief Minister of Delhi Shrimati Sheila Dikshit. | Games are free for download through the corporate social responsibility program of ZMQ | |
| South Africa | Project Masiluleke | | 276 Million text messages –one million per day – being sent (2008-2009). 1,060,000 calls answered. Messages in local languages are especially well received. | Build awareness of HIV status, encourage HIV/AIDS testing and treatment and halt the disease's spread. Stigma is a major barrier, causing people to only seek care very late in the illness. | SMS message campaign promoting HIV/AIDS awareness resulted in nearly a tripling of call volume to a local HIV/AIDS helpline. | Praekelt Foundation, iTeach, National Geographic, Nokia Siemens Networks, MTN, Ghetto Ruff, Children of South African Legacies, Aricent, PopTech!, frog design and National AIDS Helpline | 'Please Call Me' service -free text messages. 95% of South Africa uses prepaid cellular plans, and can send "please call me" message. There is 120 empty characters left in a "please call me" SMS message. | MTN has allowed program to use total inventory of "please call me" messages. |
| Uganda | Text to Change | | 15,000 mobile | HIV/AIDS awareness | 40% | Celtel, AIDs | SMS-based quiz | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | phone subscribers in rural Uganda sent the quiz in the three month pilot test | via an SMS-based multiple choice quiz in exchange for free airtime; correct answers provided; participants encouraged to come in for testing (fee waived for participants) | increase in the number of patients who came in for HIV/AIDS testing. Actionable insight: Many quiz takers did not think AIDS testing was accurate nor anonymou. | Information Centre (AIC), Merck, and the Dutch Ministry of Foreign Affairs | in exchange for free airtime | |
| Uganda, Tanzania and Kenya in Eastern Africa, and Malawi, Mozambique and Namibia in Southern Africa | Freedom HIV/AIDS Africa Reach Program [30] [31] | 2006 | In the first phase, ZMQ launched four games on Reliance Infocomm - one of the largest mobile operators of India and was able to reach out to over 9 million handsets. Later, the games were made available on other mobile carriers taking to 30 million handsets. In a span of 15 months, there have been a download of 10,3 million game sessions | Freedom HIV/AIDS introduced two HIV/AIDS awareness games to countries in Africa. Apart from English, the games have been developed in local languages - Swahili and Shen. | | Freedom HIV/AIDS is a social initiative of ZMQ Software Systems. Africa Reach Program supported by Hivos, a leading Dutch development organization, and KPN, the largest Dutch telecom company, under the "Star Programme" | Games are free for download through the corporate social responsibility program of ZMQ | |
| Many countries | FrontlineSMS | | | Free open source software that turns a laptop and a mobile phone into a central communications hub that enables users to send and receive text messages with large groups of people through mobile phones, without requiring an internet connection | | | | |
| | UNICEF/Georgia | | | | | | | |
| | Mobile4Good | | | | | | | |

## 1.13 Helpline

Helpline typically consists of a specific phone number which any individual is able to call to gain access to a range of medical services. These include phone consultations, counseling, service complaints, and information on facilities, drugs, equipment, and/or available mobile health clinics [1]

**Below is a list of mHealth Helpline projects:**

| Country | Name | Inception | Program size | Major services | Insights and Outcomes | Sponsors | Charges | Telcom partner role |
|---|---|---|---|---|---|---|---|---|
| Australia | National Health Call Centre Network or healthdirect [32] | 2007 | | | | Government-sponsored | | |
| Australia | HealthDirect (Western Australia) [32] | 1999 | | | | Government-sponsored | | |
| Australia | HealthDirect (Northern Territory) [32] | | | | | Government-sponsored | | |
| Australia | Nurse-on-Call (Victoria) [32] | 2006 | | | | Government-sponsored | | |
| Australia | HealthDirect (South Australia) [32] | 2006 | | | | Government-sponsored | | |
| Australia | Health First (Australia Capital Territory) [32] | | | | | Government-sponsored | | |
| Bangladesh | Healthline [32] | 2006 | 10000 Calls per day | Phone consults, information on facilities, drugs, test result interpretation, discounts on hospital visits. Mission: be a first reference point to complement conventional health solutions. | Top health complaints: Chronic diseases (40%), ENT, early pregnancy, malaria, pneumonia (each 8%), diarrhea (7%) | MNO-sponsored: Telemedicine firm and MNO | For profit. Service is US$ 0.21 (BDT 15) for 3 minute call | Marketing and promotion, Billing and revenue collection, Voice bearer |
| Canada | Fonemed (for USA callers) [32] | 1999 | | | | Government-sponsored | | |
| Canada | Telehealth (Ontario) [32] | 2001 | | | | Government-sponsored | | |
| Colombia | Telemedic [32] | | | | | Independent | | |
| Dominican Republic | Telemed [32] | | | | | Independent | | |
| India | HMRI [32] | 2007 | 50000 Calls per day | Phone consults, counseling and complaints, information on facilities, drugs, | Top health complaints: Recurring abdominal pain (13%), back | Government-sponsored: Government and a private charity | Not for profit. Service is free. | Voice bearer |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | mobile health clinics (vans). Mission: create platform to enable 1 billion virtual and 1 billion physical service contacts. | pain (9%), knee pain (8%) | | | |
| Mexico | Telemedic [32] | | | | | Independent | | |
| Mexico | MedicallHome [32] | 1998 | 10000 Calls per day | Phone consults, information on facilities, drugs, discounts at clinics, pharmacies. Mission: be the first choice in private health services. | | Independent: Call center entrepreneurs | For profit. Subscription: unlimited calls for US$ 5.00 monthly | Shareholder, Billing and revenue collection, Voice bearer |
| New Zealand | Healthline [32] | 2006 | | | | Government-sponsored | | |
| Pakistan | Teledoctor [32] | 2008 | 1000 Calls per day | Phone consults, information on facilities, drugs. Mission: provide cheap, easy access to experienced doctors. | Top health complaints: Diarrhea and vomiting (gastro-enteritis), Gynecological ailments and obstetrics, Fever (usually associated with respiratory tract infections) | MNO-sponsored: Telemedicine firm and MNO | For profit. Service is US$ 0.30 (PKR 24) for 3 minute call | Marketing and promotion, Billing and revenue collection, Voice bearer |
| Philippines | Fonemed Asia-Pacific [32] | planned | | | | Independent | | |
| South Africa | Eastern Cape Health Call Centre [32] | 2007 | | | | Government-sponsored | | |
| Trinidad and Tobago | MedStar Health Information [32] | 2004 | | | | Independent | | |
| United Kingdom | NHS Direct [32] | 1999 | | | | Government-sponsored | | |
| United States | MedicareBlue PPO [32] | | | | | Healthcare provider-sponsored | | |
| United States | FirstHelp Nurse Advice Line [32] | | | | | Healthcare provider-sponsored | | |
| United States | Telemed (Puerto Rico) [32] | | | | | Independent | | |
| United States | Informed Health Line (Aetna) [32] | | | | | Healthcare provider-sponsored | | |
| United States | Teladoc [32] | 2007 | | | | Independent | | |
| United States | MedicallHome USA [32] | | | | | Independent | | |

## 1.14 Diagnostic support, treatment support, communication and training for healthcare workers

Diagnostic and treatment support systems are typically designed to provide healthcare workers in remote areas advice about diagnosis and treatment of patients. While some projects may provide mobile phone applications—such as a step-by-step medical decision tree systems—to help healthcare workers diagnosis, other projects provide direct diagnosis to patients themselves. In such cases, known as telemedicine, patients might take a photograph of a wound or illness and allow a remote physician diagnose to help treat the medical problem. Both diagnosis and treatment support projects attempt to mitigate the cost and time of travel for patients located in remote areas[1]

mHealth projects within the communication and training for healthcare workers subset involve connecting healthcare workers to sources of information through their mobile phone. This involves connecting healthcare workers to other healthcare workers, medical institutions, ministries of health, or other houses of medical information. Such projects additionally involve using mobile phones to better organize and target in-person training. Improved communication projects attempt to increase knowledge transfer amongst healthcare workers and improve patient outcomes through such programs as patient referral processes[1]

Below is a list of mHealth projects for both diagnostic and treatment support, and communication and training for healthcare workers

| Country | Name | Inception | Program size | Major services | Insights and Outcomes | Sponsors | Charges | Telcom partner role |
|---|---|---|---|---|---|---|---|---|
| India | Tele-Doc [33] [30] | 2003 | Launched as a pilot project in 15 villages in Haryana in April 2003 | TeleDoc provided handheld mobile phone devices to village health workers in India, permitting them to communicate with doctors who use a web application to help diagnose and prescribe for patients. | | TeleDoc was a project of Jiva Institute, an India-based non-profit. Supported by the Soros Foundation. | The approximate cost of the entire TeleDoc process was 70 rupees (US$1.50) per consultation. | |
| Peru | Nacer [30] [34] | | | Nacer is a phone- and web- based information and communication system for maternal and child health that allows health professionals in remote locations to communicate and exchange critical health information between themselves, medical experts, and regional hospitals. All reported data is recorded in a central database, and is available to health officials in real-time for analysis and decision-making. Health workers in locations without Internet connectivity can access the system using any phone (satellite, fixed-line, mobile, or community pay phone). | | The USAID-funded Pathfinder International program and Voxiva worked with the Regional Health Directorate of Ucayali and the Peru Ministry of Health | | |
| Rwanda | TRACnet [30][35] | | | TRACnet is Rwanda's dynamic Information Technology solution designed to collect, store, retrieve, and disseminate critical program, drug, and patient information related to HIV/AIDS care and treatment. The system was | | Voxiva and The Rwanda Ministry of Health | | |

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| | | | | implemented to support the Rwandan Government's vision of rapidly scaling up HIV/AIDS clinical services in a variety of health care settings. Under the leadership of the Ministry of Health and the Treatment Research and AIDS Centre (TRAC), TRACnet is being deployed to increase the efficiency of Rwanda's HIV/AIDS program management, and enhance the quality of patient care. | | | | |
| Uganda, Mozambique | AED Satellife [30] [36] | | | Information and communications technologies (ICT) initiatives through the USA-based not-for-profit Academy for Educational Development providing support for HIV/AIDS, malaria, child and maternal health, and health systems management programs. | | | | |

### 1.15 Disease surveillance and epidemic outbreak tracking

Projects within this area operate to utilize mobile phones' ability to transmit data quickly, cheaply, and relatively efficiently. Data concerning the location and levels of specific diseases (such as malaria, HIV/AIDS, TB, Avian Flu) can help medical systems or ministries of health or other organizations identify outbreaks and better target medical resources to areas of greatest need. Such projects can be particularly useful during emergencies, in order to identify where the greatest medical needs are within a country[1]

Below is a list of mHealth disease and epidemic outbreak tracking projects:

| Country | Name | Inception | Program size | Major services | Insights and Outcomes | Sponsors | Charges | Telcom partner role |
|---|---|---|---|---|---|---|---|---|
| Brazil | Name? | | 400 test results gathered by 20 field professionals in two days, all with GPS information | Containing the spread of the Dengue virus. Customized questionnaires distributed to field health agents' mobile phones. Health data and GPS location information are integrated to enable immediate analysis and identification of areas with high infection levels. | Data collection times dramatically reduced (paper-based system would have taken 2–3 months for lesser information) . End-user acceptance very high. | Nokia, Amazonas State Health Ministry | | |
| | AESSIMS [30][38] | | | AESSIMS is designed to build health capacity at the field level by enabling front-line health workers to report disease incidence through an innovative combination of telephone and web based technology | | PATH, Voxiva, and the Governme nt of Andhra Pradesh (GoAP) | | |

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| | | | | that leverages available infrastructure. AESSIMS enables health officials to better understand the scope of disease impact and strategically allocate resources to areas with the highest prevalence and need. | | | | |
| Kenya and worldwide | EpiSurveyor.org | 2003 | Since moving from older, PDA-based version to online version, more than 2300 users from hundreds of organizations in more than 120 countries have uploaded more than 62,000 completed data records from phones (updated stats here) | EpiSurveyor is an online system developed by DataDyne.org that **allows rapid development of forms which can then be downloaded to mobile phones for data collection**: user can go from concept to fully functional mobile data collection system in hours. Used in more than 120 countries worldwide for outbreak investigation, disease surveillance, drug stock tracking . . . as well as health and economic surveys, veterinary studies, even the tracking of mountain gorillas in Uganda: if you are | Major insight: if you make an easy-to-use tool available to anyone online, many people will find and use it. EpiSurveyor is not a "project" or a "pilot": it is a fully, functional system for creating mobile data collection systems, and it is available to anyone, for free, right now. "Like Gmail for data collection" :-) | Developed with funding from the United Nations Foundation, the Vodafone Foundation, and the World Bank | Basic service, used by 99% of users, is completely free and requires "no money, no meetings, and no MOU". Premium version available. More info | |

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| | | | | collecting data on paper, you could be using EpiSurveyor, regardless of the topic. Development and support based in Nairobi, Kenya. Winner of Wall Street Journal Technology Innovation Award, Lemelson-MIT Award for Sustainability, Stockholm Challenge Award, and Tech Museum Award, and covered by Wired, the Economist, the Guardian, Voice of America, and others. | | | | |
| | Voxiva Health Watch [30][39] | | | Voxiva HealthWatch is an integrated surveillance platform used by public health agencies around the world to support integrated disease surveillance, syndromic surveillance, and coordinated response. | | | | |
| | InSTEDD | | | | | | | |

## 1.16 Treatment support and medication compliance for patients, including chronic disease management

Remote monitoring and treatment support allows for greater involvement in the continued care of patients. Within environments of limited resources and beds—and subsequently a 'outpatient' culture—remote monitoring allows healthcare workers to better track patient conditions, medication regimen adherence, and follow-up scheduling. Such projects can operate through either one- or two-way communications systems. Remote monitoring has been used particularly in the area of medication adherence for AIDS and diabetes [1]

Below is a list of mHealth treatment support and remote monitoring projects:

| Country | Name | Inception | Program size | Major services | Insights and Outcomes | Sponsors | Charges | Telcom partner role |
|---|---|---|---|---|---|---|---|---|
| Kenya | Weltel[40] | 2008 | 1 year clinical trial. ~500 participants. | HIV-positive patents were sent weekly text messages inquiring about their well-being. Patients responded to these message by saying everything was OK, or they had a problem. If there was a problem, a Health Worker would call back to assist them. | Positive results showing that mobile phones can be a useful tool in supporting HIV-positive patients. | The US Centers for Disease Control and Prevention (CDC) - PEPFAR Public Health Evaluation (PHE) and the International Development Research Centre's Africa Health Systems Initiative Support to African Research Partnerships (AHSI-RES) | | |
| Mexico | Diabediario | | | Voxiva, along with ICS, has developed Diabediario, a solution for changing diabetics' lifestyles and for controlling and improving their adherence to their diabetic treatment. Any diabetic person, who has a TelCel cell phone, can participate in the program. Diabediario uses telecommunication to generate changes in attitude towards risk | | Voxiva has partnered with the Instituto Carso de la Salud (ICS) | | |

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| | | | | prevention and adherence to prescribed treatments. Diabediario does not replace doctor's visits or pills but is meant to act as a supplement to outside care. This system empowers the patient to take control of their health by taking all the necessary steps to control their diabetes. | | | | |
| Peru | Cell-Preven [1] | | | Cell-Preven health workers use mobile phones to send SMS messages with real-time data on symptoms experienced by clinical trial participants. This enables immediate response to adverse symptoms | | Powered by Voxiva | | |
| Thailand | Name? [1] | | | TB patients were given mobile phones and called daily with a reminder to take their TB medication | 90% of patients took their medication. | | | |
| United States | mCare | 2009 | | US Army Medical Department mobile phone messaging application for the case management of reintegrated wounded soldiers. SMS-based wellness tips, appointment reminders for US service members returning from duty. Ported content from "afterdeployment.org" to a cell phone. HIPAA compliant. | | US Army Medical Department | | |
| ? | DIMA Dietary Intake Monitoring Application | 2009 | 6-week pilot study with 20 participants. | Mobile health application for dietary insight for a chronically Ill, low-literacy diabetic population | The device has a voice recorder and a bar code scanner. By the end of the study the participants were only using the voice recorder. Patients use "beam" bar code scanner more easily than pen bar code scanner. The device was not stigmatizing, rather seen as a | | | |

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| | | | | | status symbol. | | | |
| United States | Web-based Mobile Support for the Washington D.C. Tobacco Quitline | 2009 | | Currently updating the system to take real time patient smoking cessation data and "close the loop" feedback to improve adherence. Adding web interface to integrate with telephone quitline | Many behavior change things are characterized by success and relapse. Measuring real time behavior, along with context and psychological factors. "Are you feeling happy?" | Legacy Foundation | | |
| United States | MAHI Mobile Access to Health Information | 2009 | 49 participants, recently diagnosed with diabetes. 5 month study. | Each time a diabetic patient used a glucose meter the phone would give them a call to gather data on why they were using it. Nokia or any java-enabled cell phone. Used bluetooth glucose meter. ndividuals record several messages per day. Data that were typically collected: pictures of food, pictures of confusing food labels, voice notes with specific problems. | Outcomes: significant fraction of participants switched from "external" to "internal" locus of control, which meant they felt more in charge. Participants became better problem solvers with the condition, and better achieved dietary goals. | Georgia Tech, CDC, Google Health, Siemens Corporate Research | | |
| | Virtual Health Pet [30] | | | | | | | |
| | On-Cue [30] | | | | | | | |
| | SIMpill [30] | | | SMS appliance that monitors medicine compliance by sending a text message when the patient takes medicine. | | | | |
| | Cell-Life [30] | | | SMS data gathering applications | | | | |

### 1.17 Remote data collection

Policymakers and health providers at the national, district, and community level need accurate data in order to gauge the effectiveness of existing policies and programs and shape new ones. In the developing world, collecting field information is particularly difficult since many segments of the population are rarely able to visit a hospital, even in the case of severe illness. A lack of patient data creates a arduous environment in which policy makes can decide where and how to spend their (sometimes limited) resources. Projects within this area aim to link hospitals and healthcare workers with central data collectors—typically a ministry of health—that house and utilize the information. Patient data is also a vital component of this area, attempting to maintain better records of patients within health management information systems (HMIS)

### 1.18 Emerging trends and areas of interest in mHealth

- Emergency response systems (e.g., road traffic accidents, emergency obstetric care)
- Human resources coordination, management, and supervision
- Mobile synchronous (voice) and asynchronous (SMS) telemedicine diagnostic and decision support to remote clinicians[41]
- Clinician-focused, evidence-based formulary, database and decision support information available at the point-of-care[41]
- Pharmaceutical Supply Chain Integrity & Patient Safety Systems (e.g. mPedigree) [42]
- Clinical care and remote patient monitoring
- Health extension services
- Health services monitoring and reporting
- Health-related mLearning for the general public
- Training and continuing professional development for health care workers
- Health promotion and community mobilization
- Support of long-term conditions

According to Vodafone Group Foundation on February 13 2008, a partnership for emergency communications was created between the group and United Nations Foundation. Such partnership will increase the effectiveness of the information and communications technology response to major emergencies and disasters around the world.

# Chapter2:

# Artificial Intelligence in Medicine

THE STEADY expansion of medical knowledge has made it more difficult for the physician to remain abreast of medicine outside a narrow field. Consultation with a specialist is a solution when the clinical problem lies beyond the physician's competence, but frequently expert opinion is either unavailable or not available in a timely fashion. Attempts have been made to develop computer programs that can serve as consultants (1-3). By the early 1970s it became clear that conventional tools such as flow charts, pattern matching, and Bayes' theorem were unable to deal with most complex clinical problems (4). Investigators then began to study the expert physician to obtain detailed insights into the basic nature of clinical problem solving (5-8). The results derived from such studies have subsequently formed the basis for computational models of the cognitive phenomena, and these models have further been converted into so-called artificial intelligence programs (9-12).

Many of the early efforts to apply artificial intelligence methods to real problems, including medical reasoning, have primarily used rule-based systems (13). Such programs are typically easy to create, because their knowledge is catalogued in the form of "if ... then..." rules used in chains of deduction to reach a conclusion. In many relatively well-constrained domains rule-based programs have begun to show skilled behavior (14). This is true in several narrow domains of medicine as well (14, 15), but most serious clinical problems are so broad and complex that straightforward attempts to chain together larger sets of rules encounter major difficulties. Problems arise principally from the fact that rule-based programs do not embody a model of disease or clinical reasoning. In the absence of such models, the addition of new rules leads to unanticipated interactions between rules and thus to serious degradation of program performance (16-18).

Given the difficulties encountered with rule-based systems, more recent efforts to use artificial intelligence in medicine have focused on programs organized around models of disease. Efforts to develop such programs have led to substantial progress in our understanding of clinical expertise, in the translation of such expertise into cognitive models, and in the conversion of various models into promising experimental programs. Of equal importance, these programs have been steadily improved through the correction of flaws shown by confronting them with various clinical problems.

We will focus on how improved representation of clinical knowledge and sophisticated problem-solving strategies have advanced the field of artificial intelligence in medicine. Our purpose is to provide an overview of artificial intelligence in medicine to the physician who has had little contact with computer science. We will not concentrate on individual programs; rather, we will draw on the key insights of such programs to create a coherent picture of artificial intelligence in medicine and the promising directions in which the field is moving. We will therefore describe the behavior not of a single existing program but the approach taken by one or another of the many programs to which we refer. It remains an important challenge to combine successfully the best characteristics of these programs to build effective computer-based medical expert systems. Several collections of papers (19-21) provide detailed descriptions of the programs on which our analysis is based.

### 2.1 A Basic Program for Clinical Problem-Solving

Any program designed to serve as a consultant to the physician must contain certain basic features. It must have a store of medical knowledge expressed as descriptions of possible diseases. Depending on the breadth of the clinical domain, the number of hypotheses in the database can range from a few to many thousands. In the simplest conceivable representation of such knowledge, each disease hypothesis identifies all of the features that can occur in the particular disorder. In addition, the program must be able to match what is known about the patient with its store of information. Even the most sophisticated programs typically depend on this basic strategy.The simplest version of such programs operates in the following fashion when presented with the chief complaint and when later given additional facts.

1. For each possible disease (diagnosis) determine whether the given findings are to be expected.

2. Score each disease (diagnosis) by counting the number of given findings that would have been expected.

3. Rank-order the possible diseases (diagnoses) according to their scores.

The power of such a simple program can be greatly enhanced through the use of a mechanism that poses questions designed to elicit useful information. Take, for example, an expansion of the basic program by the following strategy:

4. Select the highest-ranking hypothesis and ask whether one of the features of that disease, not yet considered, is present or absent.

5. If inquiry has been made about all possible features of the highest-ranked hypothesis, ask about the features of the next best hypothesis.

6. If a new finding is offered, begin again with step 1; otherwise, print out the rank-ordered diagnoses and their respective supportive findings and stop.

Steps 1 through 3 contain a primitive evaluation of the available information, and steps 4 through 6 contain an equally simple information-gathering strategy that determines what information to seek next. But such a program fails to capture many of the techniques responsible for expert performance. For example, the ranking process does not take into account how frequently particular features occur in a given disease. The program, furthermore, has no knowledge of pathophysiology and is not able to take stock of the severity of an illness. The most serious problem is that each new finding sets into motion a search process tantamount to considering all disease states appearing in a textbook of medicine. Even for a high-speed computer this is not a practical diagnostic strategy and for this reason research has turned to the study of how experts perform.

## 2.2 From Cognitive Models to Computer Programs

The physician's ability to sharply limit the number of hypotheses under active consideration at any one time is a key element in expert performance (5, 6, 9). Computer programs that use the strategies of experts can accomplish this same goal and devote the bulk of their computational resources to the sophisticated evaluation of a small number of hypotheses.

Controlling the proliferation of hypotheses is only the first step in creating effective artificial intelligence programs. To deal with the circumstance in which one disease influences the clinical presentation of another, the program must also have the capacity to reason from cause to effect. Moreover, the required pathophysiologic knowledge must be organized in a hierarchical fashion so that the information becomes more detailed as one progresses to deeper levels of the knowledge base. Quantitative information, or rough qualitative estimates, must also be added to the causal links if the program is to separate the contribution of each of several disorders to a complex clinical picture.

The cognitive models that embody these principles provide the basis for computer programs that use the chief complaint and other available information to reduce the range of diagnostic possibilities. The narrowing process can be viewed as passive in that the program makes all possible progress without requesting further facts. The passive phase completed, the program moves to an active mode of posing questions to the physician. This process is interactive with each new fact stimulating additional analysis that further reduces the number of diagnostic possibilities. In the following discussion, attention will be directed primarily to the passive narrowing process because this strategy plays a central role in clinical problem solving and because more is known about this process than about the active collection of new information.

### 2.3 Passively Processing the Available Information

One simple technique for limiting the number of active hypotheses consists of selecting from a large database only those disorders for which there is evidence in the chief complaint. Limiting activation in this way is useful but rarely restricts the number of hypotheses to a small handful, typically three or four. An alternative and often more effective strategy called triggering allows activation only in response to a finding highly suggestive of a particular disease (9). For example, a history of vomiting blood will trigger "peptic ulcer" as an hypothesis; by contrast, the complaint of an occasional headache will not trigger "brain tumor." In this scheme, findings other than triggers are used in the diagnostic process only when a particular hypothesis has already been activated. Unfortunately, even in this strategy a single trigger frequently generates an unmanageably large set of hypotheses (22, 23). But, by using two findings, the behavior of the activation mechanism can often be improved. For example, the joint findings of hematuria and proteinuria can be used to activate a much narrower set of hypotheses than will either finding alone. Adding more elements to the trigger will further restrict the number of hypotheses that are activated, but the gain is sometimes achieved at a price; if a finding is improperly included in the trigger or a relevant finding is ignored, the possibility of a diagnostic error is considerably increased. Experimental evidence suggests that a cluster of two or three findings provides the right balance between specificity and the risk of missing a diagnosis (24).

Facts obtained during the questioning phase may activate new hypotheses but frequently they also argue against diagnoses already under consideration. The new fact may be incompatible with a given hypothesis, such as a massive amount of protein in the urine of a patient

suspected of having uncomplicated chronic pyelonephritis, or it may argue indirectly against a disease by strongly favoring a competing one. Under either circumstance, the hypothesis can be removed from active consideration (9). Even a newly activated hypothesis can immediately be deactivated if facts already available argue strongly against it.

Deactivation does not permanently exclude a hypothesis from consideration; the hypothesis may be reactivated if additional supportive information is later obtained or if it must be explicitly ruled out in order to confirm some other diagnosis (9).

Even when the triggering process is combined with a mechanism for deactivation, it may not adequately control the proliferation of hypotheses. Under such circumstances, the diseases under consideration can be reduced in number by grouping those of similar character (such as kidney diseases or infectious diseases) into a single hypothesis known as an aggregate. Such a structure incorporates all of the findings that occur with particular frequency in the cluster of diseases forming the aggregate. An aggregate cannot only stand in lieu of an unmanageably large number of diseases but can be organized into a hierarchy that facilitates analysis of the diagnostic problem. The top level aggregate of such a hierarchy contains all disorders under suspicion, and each lower level contains the same disorders divided into successively smaller clusters. The program can then choose one of several strategies to select the level within the hierarchy that provides the best focus for subsequent questioning.

**Intermixed hierarchies:** The first hierarchies used by artificial intelligence programs were intermixed in character (12, 25); each level in the hierarchy was organized around a different disease characteristic such as duration of illness (acute or chronic), anatomical site, etiology, and so forth. In such a hierarchy, the program must explore the sequence of characteristics in a predetermined fashion, typically from top to bottom or vice versa. But in many cases adherence to such a predetermined sequence will force the program into a grossly inefficient pattern of questioning and lead to poor diagnostic performance. Still another defect is that intermixed hierarchies cannot deal with multisystem diseases such as lupus erythematosus, scleroderma, or periarteritis nodosa (26).

**Pure hierarchies:** Because of these deficiencies, attention has shifted towards the use of so-called pure hierarchies that incorporate only a single disease characteristic. A pure hierarchy for kidney diseases, for example, might be based on the anatomical site of involvement. Individual proximal and distal tubular diseases that appear at the lowest level of the hierarchy

can be organized into an aggregate embodying all tubular diseases, and similar aggregates can be created for glomerular, interstitial, and vascular diseases. These aggregates can then be brought to a higher level encompassing all kidney diseases. Such a structure can also be expanded to include nonrenal disorders.

Because a pure hierarchy has only a single organizing theme, the program can move across levels without difficulty and focus quickly on the level that merits further consideration. On the other hand, a diagnostic strategy based on use of a single pure hierarchy is of no value when exploration of more than one clinical characteristic is required. This limitation has caused investigators to shift their attention to the use of multiple pure hierarchies. (27, 28).

**Reasoning with multiple pure hierarchies***:* Multiple pure hierarchies allow a program to explore a wide range of disease characteristics while preserving ease and clarity of analysis. Consider a patient who has ingested a poison and is also oliguric. Multiple pure hierarchies allow the program to focus on those aspects of the patient's condition most relevant to each significant initial fact, in this case identifying the cause of the illness and its pathophysiologic consequences as the prime issues, and then to integrate its understanding of the different aspects of the case into an overall conclusion. First, the program takes all of the available facts and searches through each hierarchy to identify the smallest set of hypotheses that it can validate; second, it searches across the subsets drawn from each hierarchy to identify the diagnostic possibilities most worth pursuing.

Reasoning within an individual hierarchy can be accomplished by one of two means. The top-down Strategy is most appropriate when little specific information is initially available, so that the most efficient approach consists of moving from the general to the specific. The top-down strategy uses scoring methods to determine the goodness-of-fit between the observed manifestations and the highest-level disease hypothesis in a given hierarchy. If the hypothesis is found to be valid by some particular set of criteria, the program moves to the next level where there are two or more aggregates, each encompassing a narrower range of diseases. If any one or several aggregates are found to be valid, the entire process is repeated until a level is reached below which either validity cannot be shown or the total number of alternative hypotheses (usually four or five) becomes too large.

The bottom-up strategy is best used when the findings suggest a large number of specific diseases but do not provide an organizing theme around which to formulate a differential

diagnosis. The bottom-up strategy is initiated by a triggering mechanism that selects the individual hypotheses that merit consideration. If these hypotheses cannot be distinguished from one another on the basis of available information, the program moves to a higher level in the hierarchy; this move is accomplished by replacing each group of individual diseases by the aggregate encompassing them.

After having chosen the prime set of diagnostic possibilities within each hierarchy, the program moves into the second phase in which it looks across the subsets to identify those diseases on which further questioning should focus. These diseases are found by identifying those disorders that appear in two or more subsets (27). For example, in the oliguric patient who is known to have ingested a poison, the intersection between the prime disease sets in the anatomic and etiologic hierarchies will yield a tentative diagnosis of acute renal failure of nephrotoxic origin. In more complex cases, several diseases will emerge from this process. The computation of such an intersection, although seemingly simple, is a fairly complex programming task. Skilled physicians, on the other hand, carry out this process rather easily, probably because they have previously explored so many search paths that they know in advance the answers. A similar pre-exploration has recently been exploited to good effect in programs that make use of several hierarchies (27).

**2.4 Dealing with Multiple Disorders**

The strategies thus far considered assume that the patient has one disease. If several disorders are present, the problem is more complex. Additional difficulties arise if the several possible diseases have findings in common or if one disorder influences the presentation of another. The challenge posed by several disorders pushes existing artificial intelligence programs to their conceptual and computational limits.

Nearly all early programs that dealt with several disorders were successful in diagnosing only diseases without overlapping findings. These programs assumed that all hypotheses were competitors and attempted to identify the single most likely diagnosis (22). Only after the first diagnosis was confirmed did they attempt to make a second diagnosis based on the residual findings, a process that was repeated as long as there were findings not accounted for by an already confirmed diagnosis. Such a sequential approach contains a major flaw: because the program initially has no way of recognizing that more than one disorder exists, findings that are not relevant to the primary disorder can easily confound the diagnostic

process. For example, in a patient with both chronic glomerulonephritis and an acute myocardial infarction, the program will try to attribute all clinical manifestations to each disease. It may, therefore, dismiss the diagnosis of chronic glomerulonephritis simply because it cannot account for severe chest pain.

A partial solution to this problem can be achieved if one assumes that coexisting disorders should, in general, account for a larger set of observed findings than either alone. The Internist-l program (12) exploits this idea. First, all active hypotheses are rank-ordered and the leading hypothesis is taken as the focus of the diagnostic process; any diseases that account for findings not already explained by the leading hypothesis are removed from the active list and put aside for later consideration. The hypotheses remaining on the active list are considered competitors of both the leading hypothesis and each other. The program then pursues various standard strategies for information gathering to arrive at a diagnosis. It then subsequently turns to the disorders that have been set aside earlier and carries out the same process of differential diagnosis.

This ability to partition the sets of diseases and findings is the key to Internist- l's ability to diagnose correctly many of the cases drawn from clinico-pathologic conferences (12, 27). But even such a partitioning algorithm

cannot deal with two diseases whose findings overlap appreciably. If all observed findings are common to both diseases, the program will incorrectly consider the two to be competitors. Thus after confirming the presence of one disease, it will ignore the other because all shared findings have been accounted for. Moreover, the program cannot deal with one disorder that has altered the clinical presentation of another (29). Consider a patient with acute renal failure of some days' duration whose illness is complicated by severe vomiting. If the serum potassium concentration was normal or low and the program expected an elevated serum potassium level, the program would not be able to make the correct diagnosis.

To deal with diseases whose findings overlap or interact, a program's best strategy is to use pathophysiologic reasoning that links diseases and findings through a network of causal relations. Through this mechanism, which emulates expert human performance, the program can create a composite hypothesis that attempts to explain all of the clinical findings. If several combinations of diseases are consistent with available information, several competing composite hypotheses must be constructed. This process cannot be done in the same fashion

as with individual disease hypotheses. Descriptions of individual diseases can be created in advance and made available on demand. Potential composite hypotheses, because they are extremely large in number, must instead be fashioned on an individual basis from the findings in a particular case.

The core of a composite hypothesis for a given patient is constructed by bringing together the set of abnormal states (such as pulmonary insufficiency, hypertension, acidosis) that make up the overall clinical picture (28). To this core are added its possible underlying causes and the mechanisms that bring about its clinical manifestations. A representative composite hypothesis is shown in level I of Figure 1, which shows the simplest causal network accounting for the acidosis and hypokalemia induced by a combination of severe diarrhea and a moderate degree of vomiting. Each possible explanation for the electrolyte disorders, such as renal failure or diabetic ketoacidosis, is represented in the program as a competing composite hypothesis. If no single cause adequately accounts for the severity of all the findings, the program will conclude that more than one cause must be present. The program then uses pathophysiologic reasoning to estimate the effects of interactions among the possible causes. Interactions among diseases can be estimated more precisely by supplementing the causal links with quantitative information describing the magnitude of each cause and effect (29, 30).

Even rough qualitative estimates (such as slight, moderate, or severe) can assist in determining whether a single diagnosis is consistent with known findings (31, 32). If, for example, a patient with mild congestive heart failure is found to have massive edema, the program will suspect that a second disorder (such as the nephrotic syndrome) is present. If additional evidence supporting a second cause can be found, it will be added to the composite hypothesis. If no such explanation is forthcoming, the program will consider laboratory error or a faulty patient history.

The more detailed the causal reasoning, the greater the price in terms of computational costs. Such costs can be minimized, however, by organizing knowledge into layers of increasing detail. A system based on such a knowledge base can select the most appropriate level at which to operate, using efficient, shallow reasoning in simple cases and resorting to expensive, detailed reasoning only when there is no alternative (28). A small hierarchical composite hypothesis, showing three levels of detail, is shown in Figure 1 (28). The shallow reasoning of level I, described earlier, is more fully elaborated by level II, which shows the

homeostatic adjustments in a patient with diarrhea and vomiting. Level III provides a more detailed description of how the organism responds to gastrointestinal losses.

Many of the ideas discussed thus far have been tested in experimental programs, but no program has yet succeeded in integrating the various mechanisms required to produce a useful and reliable expert consultant.

### 2.5 Information Gathering and Reaching Diagnostic Conclusions

Once the passive component of the program has reduced the number of hypotheses as much as possible, the active mode of questioning begins. The diagnostic strategies confirm, eliminate, and differentiate are derived, as in the first portion of the program, from analysis of expert performance (5, 6, 12). The choice of a particular strategy is based on the following criteria. If a single hypothesis is the leading candidate by a wide margin, the program will gather data designed to confirm the diagnosis or at least to give it further credence. If no such data can be obtained readily and safely, the program will try to elicit information that can eliminate one or more of the competing diagnoses. Differentiation, the last of the three strategies, is generally used when only two hypotheses are under active consideration; the purpose is to gather information that favors one diagnosis while arguing against the other.

In many clinical situations, however, an optimal strategy cannot be chosen using the simple criteria just described (30, 33); instead, one must develop a plan for questioning based on possible answers to the series of questions that might be posed. One recent approach consists of developing a coherent plan for information gathering based on stored knowledge of diagnostic strategies (30, 33, 34). For example, when the program is trying to differentiate between renal and essential hypertension, it would note that the diagnosis of essential hypertension is typically made by exclusion. On this basis, the program will develop a strategy designed to confirm the diagnosis of renal hypertension rather than differentiate between the two disorders. To accomplish this goal, the program will establish various sequences of possible questions and answers and then choose the line of questioning that looks most promising (4, 30).

A pathognomonic abnormality provides the easiest path to diagnosis, but such findings are extremely uncommon. Moreover, even such a finding must be viewed with caution because

of the possibility of error; corroboration of a pathognomonic finding by other data is necessary before a conclusion can be reached.

If the questioning process has been completed and the diagnosis is still in doubt, the program rank-orders the set of hypotheses still under active consideration and reports the results to the user. Several numerical scoring schemes have been used in such a scoring process but none have proved completely satisfactory. The commonest scheme quantifies the frequency with which each finding is associated with a given disease (9, 12, 22, 27) and simply sums the weights assigned to such findings. A more sophisticated version of this strategy makes formal use of Bayes' theorem (35-37). The diagnostic investigation is typically terminated when the score, or a value for the probability, has reached some predetermined threshold (9, 12, 35, 38). Available evidence indicates that humans have great difficulty in making reliable probabilistic judgments and calculations (39), suggesting that skilled physicians reach diagnostic closure by unidentified strategies.

A program may not reach a diagnostic threshold even after gathering all the useful information that can be obtained without using studies that impose risk or pain. At this point, decision analysis can be used to decide whether such studies should be done or whether treatment should be initiated even in the face of considerable uncertainty (40). The response to treatment will, of course, sometimes provide the best means of arriving at a firm diagnosis.

### *2.6 Discussion*

Most approaches to computer-assisted diagnosis have, until the past few years, been based on one of three strategies-flow charts (1, 2, 41), statistical pattern-matching (42), or probability theory (4, 35, 43, 44). All three techniques have been successfully applied to narrow medical domains, but each has serious drawbacks when applied to broad areas of clinical medicine. Flow charts quickly become unmanageably large. Further, they are unable to deal with uncertainty, a key element in most serious diagnostic problems. Probabilistic methods and statistical pattern-matching typically incorporate unwarranted assumptions, such as that the set of diseases under consideration is exhaustive, that the diseases under suspicion are mutually exclusive, or that each clinical finding occurs independently of all others (22). In theory, these problems could be avoided by establishing a database of probabilities that copes with all possible interactions (37). But gathering and maintaining such a massive database would be a nearly impossible task. Moreover, all programs that rely solely on statistical

techniques ignore causality of disease and thus cannot explain to the physician their reasoning processes nor how they reach their diagnostic conclusions.

Programs using artificial intelligence techniques have several major advantages over programs using more traditional methods. These programs have a greater capacity to quickly narrow the number of diagnostic possibilities, they can effectively use pathophysiologic reasoning, and they can create models of a specific patient's illness. Such models can even capture the complexities created by several disease states that interact and overlap. These programs can also explain in a straightforward manner how particular conclusions have been reached (33, 45). This latter ability promises to be of critical importance when expert systems become available for day-to-day use; unless physicians can assess the validity of a program's conclusions, they cannot rely on the computer as a consultant. Indeed, a recent survey has shown that a program's ability to explain its reasoning is considered by clinicians to be more important than its ability to arrive consistently at the correct diagnosis (46). An explanatory capability will also be required by those responsible for correcting errors or modifying programs; as programs become larger and more complicated, no one will be able to penetrate their complexity without help from the programs themselves.

Causal, quantitative reasoning also leads to programs that can plan and manage therapy. Past events can be used not only to predict current findings but to anticipate the possible future evolution of an illness and the consequences of particular therapeutic actions (47, 48). Such capabilities provide the framework for expanding computer programs beyond their conventional bounds as diagnostic aids.

Progress toward developing practical consulting programs has been slow despite the rapid increase in our understanding of how experts solve problems. Experience shows that 5 years is required to incorporate a new cognitive model into an artificial intelligence program and to test it adequately. Two major factors have prevented more rapid implementation. First, a large amount of detailed medical knowledge must be gathered even when one is dealing with a relatively narrow clinical domain. Second, newer cognitive models are so complex that their implementation typically poses a major technical challenge.

Even if the various problems in implementation can be solved, further obstacles will impede the development of programs that are ready for routine clinical use. Decisions must be made

concerning acceptable performance levels (1) and extensive debugging and in-hospital testing must be done to assure that the standards are being met.

Fortunately, even before the advent of fully functional computer programs that can act as sophisticated consultants on the most difficult medical problems, the fruits of artificial intelligence research can be applied in less taxing medical settings. Two recent programs, for example, combine the scoring methods of Internist-l (12) and databases that link diseases with their manifestations to generate lists of hypotheses that may be worthy of detailed consideration (49, 50). Other artificial intelligence programs applied in narrow medical domains have also proved to have practical value, in applications ranging from laboratory data interpretation to protocol-based patient management (51-53). Although only a few such programs are currently available, the evidence suggests that the continued development of artificial intelligence techniques will eventually give the computer a major role as an expert consultant to the physician.

# Chapter 3:

# Prostate Diseases

### 3.1 Anatomy of the prostate

Urologists and pathologists have focused more and more on the anatomic structures of the human prostate gland and their relationship to prostate carcinoma development and prognosis since the resurgence of radical prostatectomy in the late 1980s. The accessibility of whole-mount slide preparation in the study of the prostate has greatly simplified this analysis.

This chapter concentrates on the anatomy of the prostate gland and analyzes how anatomic structures relate to the origin, development, and evolution of prostate carcinoma. The concept of zonal anatomy and its role in prostate carcinoma will also be described.

Anatomy and histology of the normal prostate During the third month of gestation, the prostate gland develops from epithelial invaginations from the posterior urogenital sinus under the influence of the underlying mesenchyme [1].The normal formation of the prostate gland requires the presence of 5α-dihydrotestosterone, which is synthesized from fetal testosterone by the action of 5α-reductase [2]. This enzyme is localized in the urogenital sinus and external genitalia of humans [3]. Consequently, deficiencies of 5α-reductase will cause a rudimentary or undetectable prostate in addition to severe abnormalities of the external genitalia, although the epididymides, vasa deferentia, and seminal vesicles remain normal [4]. During the prepubertal period, the constitution of the human prostate remains more or less identical but begins to undergo morphologic changes into the adult phenotype with the beginning of puberty. The gland enlarges continuously in size to reach the adult weight of approximately 20 g by 25–30 years of age [1]. The base of the prostate is at the bladder neck and the apex at the urogenital diaphragm [5]. The Denonvilliers' fascia, a thin, filmy layer of connective tissue, separates the prostate and seminal vesicles from the rectum posteriorly. Skeletal muscle fibers from the urogenital diaphragm extend into the prostate at the apex and up to the midprostate anteriorly [6]. In the twentieth century, several investigators maintained that the prostate gland was composed of diverse lobes by analogy with laboratory animals [1, 7]. This concept became popular even though no distinct lobes can be seen in the human. Thereupon, McNeal established the current and most widely accepted concept Of various zones rather than lobes of the prostate [8, 9, 10].

The peripheral zone comprises all the prostatic glandular tissue at the apex as well as all of the tissue located posteriorly near the capsule (Figure 1.1). In this zone, carcinoma, chronic prostatitis, and postinflammatory atrophy are relatively morecommon than in the other zones. The central zone is a cone-shaped area of the adult gland, with the apex of the cone at the

confluence of the ejaculatory ducts and the prostatic urethra at the verumontanum (Figure 1.1). The transition zone consists of two equal portions of glandular tissue lateral to the urethra in the midgland (Figure 1.1). This portion of the prostate is involved in the development of age-related benign prostatic hyperplasia (BPH) and, less commonly, adenocarcinoma.

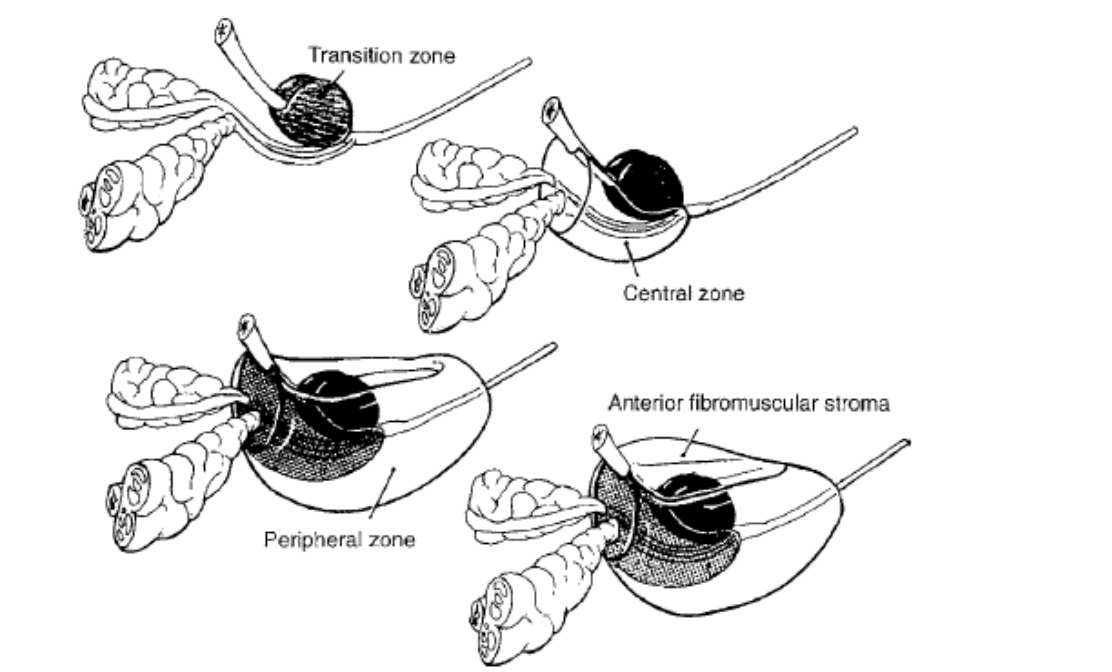
The anterior fibromuscular stroma (AFMS) forms the convexity of the anterior external surface. The apical half of this area is rich in striated muscle, which blends into the gland and the muscle of the pelvic diaphragm (Figure 1.1).

Toward the base, smooth muscle cells become predominant, blending into the fibers of the bladder neck [11]. The distal portion of the AFMS is important in voluntary sphincter functions, whereas the proximal portion plays a central role in involuntary sphincter functions.

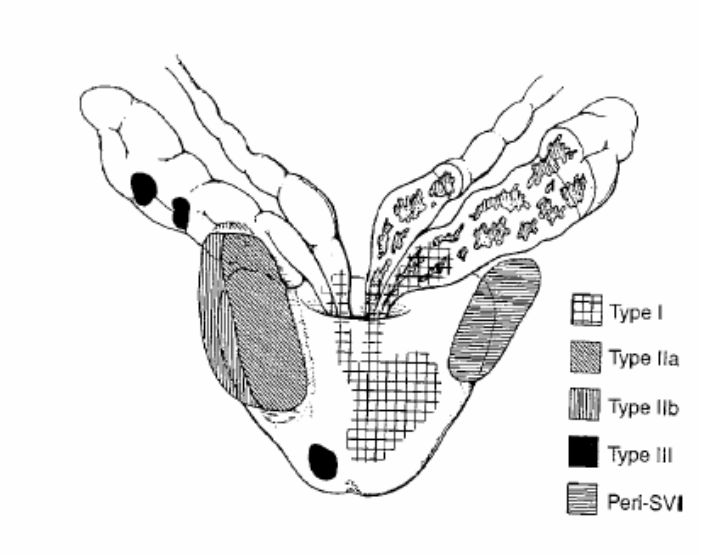
The histologic architecture of the prostate is that of a branched duct gland. Two cell layers, a luminal secretory columnar cell layer and an underlying basal cell layer, line each gland or duct. The lumens of otherwise normal prostatic glands and ducts frequently contain multilaminated eosinophilic concretions, termed corpora amylacea, that become more common in older men. Calculi are larger than those corpora with a predilection for the ducts that traverse the length of the surgical capsule, separating the transition and peripheral zones.

The prostatic capsule is composed of fibrous tissue surrounding the gland. Although the term “capsule” is embedded in the current literature and common parlance, there is no consensus about the presence of a true capsule [12]. This capsule is best appreciated posteriorly and posterolaterally as a layer more fibrous than muscular, between the prostatic stroma and extraprostatic fat. The seminal vesicles are located superior to the base of the prostate. They undergo confluence with the vas deferens on each side to form the ejaculatory ducts. The ejaculatory duct complex consists of the two ejaculatory ducts along with a second loose stroma rich in vascular spaces. The utricle (when present) is located between the ejaculatory ducts. The remnants of the utricle occasionally form cystic structures in the midline posteriorly. The seminal vesicles are resistant to nearly all of the disease processes that affect the prostate. Seminal vesicle involvement (SVI) by prostate cancer (PCa) is one of the most important predictors for PCa progression (Figure 1.2) [13, 14].

Metastatic PCa oftentimes involves pelvic lymph nodes. The prognostic significance of this feature has been documented by several investigators [15]. In some individuals, periprostatic (PP) and periseminal vesicle (PSV) lymph nodes are present and, although uncommon, they may be involved by metastatic PCa as well, sometimes in the absence of pelvic lymph node metastases [16].



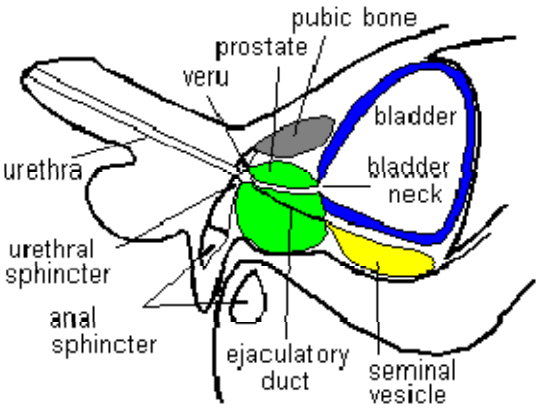

(Figure 1.1) Zonal anatomy of the normal prostate as described by McNeal [8, 9, 10]. The transition zone comprises only 5%–10% of the glandular tissue in the young male. The central zone forms part of the base of the prostate and it is traversed by the ejaculatory ducts. The prostate is constituted by the peripheral zone, particularly distal to the verumontanum. (From Greene DR, Shabsigh R, Scardino P T. Urologic ultrasonography. In: Walsh P C, Retik A B, Stamey T A et al. eds. Campbell's Urology, 6th edn. Philadephia: WB Saunders, 1992; 342–393, with permission.)

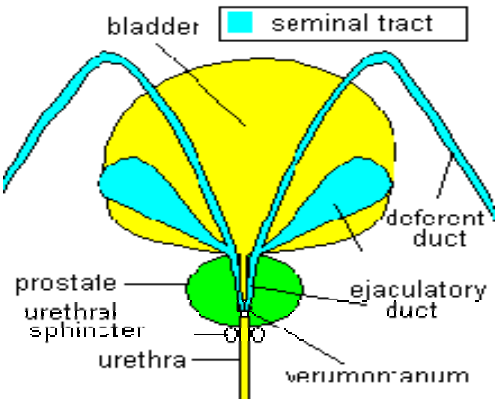



(Figure 1.2) Diagrammatic representation of the three patterns of seminal vesicle involvement (SVI) and peri-SVI. The combination of types I and II is categorized as type I + II. (From Ohori M, Scardino P T, Lapin S L et al. The mechanisms and prognostic significance of seminal vesicle involvement by prostate cancer. Am J Surg Pathol 1993; 17: 1253 [14], with permission.)

## 3.2 PHYSIOLOGY

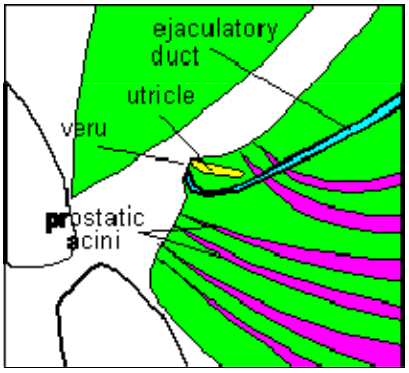
To enable us to understand the possible mechanisms leading to "chronic prostatitis" we have to know some basic facts about the physiology of the prostate

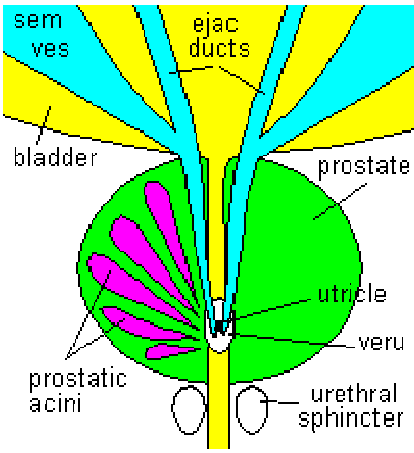


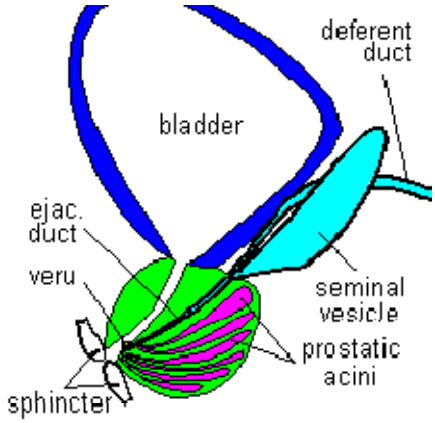
The prostate is a gland situated underneath the bladder (the **bladder neck**) and is perforated by the first portion of the urethra. The 2 **ejaculatory ducts** enter the upper part of the prostate from behind, travel through the gland and open into the urethra on a small protuberance (3-4 mm) of the urethral mucosa called the **verumontanum ("veru")**. The veru is very critical because of the convergence of several other structures:

- Between the 2 openings of the ejaculatory ducts, we find the opening of the **utricle**, a remnant of our early life as embryo (a small duct representing the rests of the tissue which in the female develops into the uterus). The appearance of the utricle can vary widely from a tiny dimple in the veru to a long narrow duct extending deep into the prostatic tissue parallel to the ejaculatory ducts in the midline. In some individuals, this duct obliterates forming a cyst (utricular cyst) in the prostate, not rarely the cause of symptoms identical to those of "chronic prostatitis".




- The prostate is composed of 25-30 small glandular units (**acini**) located in the periphery of the prostate, and each glandular unit is connected to the outside world by a tiny duct which opens into the urethra at each side in direct proximity to the veru. The prostatic acini produce a fluid that, at orgasm, is expelled from the acini by contraction of the prostatic smooth muscle tissue surrounding these acini. The composition of the prostatic fluid is vital for the well-being of the spermatic cells outside the body and severe alteration, like in certain forms of chronic prostatitis, can degrade fertility.




Other important anatomical structures, mostly neglected in the literature, are the **seminal vesicles (SV)**. These glands reside on the backside of the lower part of the bladder, their body (about 5-8 cm long, .6-1 cm wide) lies alongside the deferent duct (which carries the sperm cells from the testis to the urethra) and empties into this duct before the deferent duct enters the prostate to become the ejaculatory duct. The SVs are structurally hollow organs comparable to the gallbladder, but with multiple small saccular compartments (looking almost like a grape) interconnected with each-other. The wall of the SVs is composed of an internal cellular lining (glandular cells) which produces a fluid necessary for the extracorporeal survival of the sperm cells. This fluid, together with the fluid from the prostatic acini, constitutes a major part of the volume of the spermatic fluid; only a small part comes from the testicles. The outside muscular shell of the SVs contracts and expells the secretion at orgasm.

In summary, in a minute spot of the prostatic urethra around the veru, covering an area not larger then 1 square cm (about 1/6 square inch) we find all the openings where the spermatic secretion has to pass through. One can immagine that a slight change (focal inflammation with edema, calcifications, microscars after inflammatory disease etc) can distort, compress, obstruct (partially or completely, temporarily or definitively) those tiny openings creating all the conditions necessary for disease in one, few or many prostatic glandular subunits or the seminal tract. Of course, if passage through one or several of these ducts is not completely restored (e g due to inadequate treatment of an acute exacerbation of prostatitis, permanent changes like calcified deposits of detritus or scars) we'll have to expect chronification of the inflammatory process (not always symptomatic) with acutisation from time to time. The close relationship of the SVs and the prostate to the bladder neck and the trigone (an area in the bladder floor adjacent to the bladder neck), the most sensitive parts of the bladder with a dense concentration of sensory nerve endings, explain the occurrence of urgent desire to void frequently associated with irritative conditions in the prostate/SV. In conclusion, an comprehensive appreciation of the anatomical structures and their relationship is necessary for the understanding of the different syndromes that run under the term of "chonic prostatitis", instead of a view limited to the prostate only.

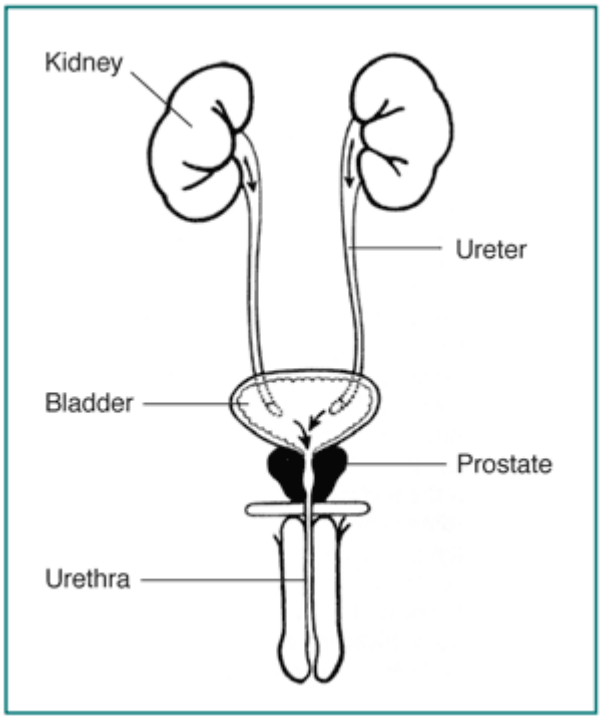
### 3.3 Diseases of  The Prostate Gland

The prostate is a walnut-sized gland that forms part of the male reproductive system. The gland is made of two lobes, or regions, enclosed by an outer layer of tissue. As the diagrams show, the prostate is located in front of the rectum and just below the bladder, where urine is stored. The prostate also surrounds the urethra, the canal through which urine passes out of the body.

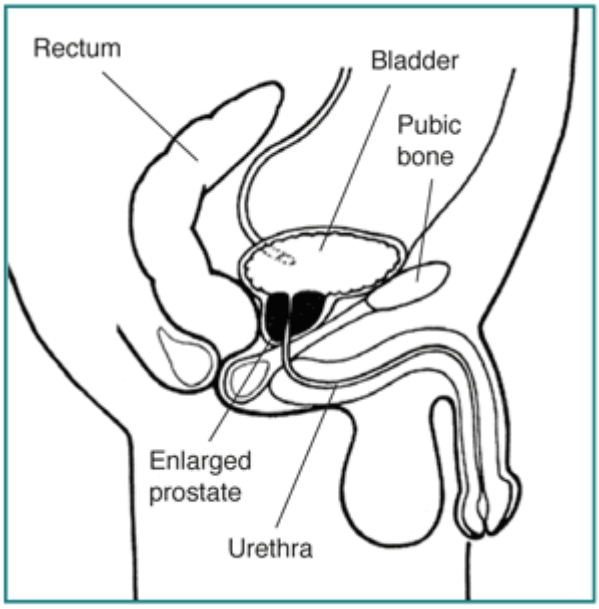
Scientists do not know all the prostate's functions. One of its main roles, though, is to squeeze fluid into the urethra as sperm move through during sexual climax. This fluid, which helps make up semen, energizes the sperm and makes the vaginal canal less acidic.

### 3.4 Benign Prostatic Hyperplasia: A Common Part of Aging

It is common for the prostate gland to become enlarged as a man ages. Doctors call this condition benign prostatic hyperplasia (BPH), or benign prostatic hypertrophy.




**Normal urine flow.**




**Urine flow with BPH.**

As a man matures, the prostate goes through two main periods of growth. The first occurs early in puberty, when the prostate doubles in size. At around age 25, the gland begins to grow again. This second growth phase often results, years later, in BPH.

Though the prostate continues to grow during most of a man's life, the enlargement doesn't usually cause problems until late in life. BPH rarely causes symptoms before age 40, but more than half of men in their sixties and as many as 90 percent in their seventies and eighties have some symptoms of BPH.

As the prostate enlarges, the layer of tissue surrounding it stops it from expanding, causing the gland to press against the urethra like a clamp on a garden hose. The bladder wall becomes thicker and irritable. The bladder begins to contract even when it contains small amounts of urine, causing more frequent urination. Eventually, the bladder weakens and loses the ability to empty itself, so some of the urine remains in the bladder. The narrowing of the urethra and partial emptying of the bladder cause many of the problems associated with BPH.

Many people feel uncomfortable talking about the prostate, since the gland plays a role in both sex and urination. Still, prostate enlargement is as common a part of aging as gray hair. As life expectancy rises, so does the occurrence of BPH. In the United States in 2000, there were 4.5 million visits to physicians for BPH.

### 3.5 Why BPH Occurs

The cause of BPH is not well understood. No definite information on risk factors exists. For centuries, it has been known that BPH occurs mainly in older men and that it doesn't develop in men whose testes were removed before puberty. For this reason, some researchers believe that factors related to aging and the testes may spur the development of BPH.

Throughout their lives, men produce both testosterone, an important male hormone, and small amounts of estrogen, a female hormone. As men age, the amount of active testosterone in the blood decreases, leaving a higher proportion of estrogen. Studies done on animals have suggested that BPH may occur because the higher amount of estrogen within the gland increases the activity of substances that promote cell growth.

Another theory focuses on dihydrotestosterone (DHT), a substance derived from testosterone in the prostate, which may help control its growth. Most animals lose their ability to produce DHT as they age. However, some research has indicated that even with a drop in the blood's testosterone level, older men continue to produce and accumulate high levels of DHT in the prostate. This accumulation of DHT may encourage the growth of cells. Scientists have also noted that men who do not produce DHT do not develop BPH.

Some researchers suggest that BPH may develop as a result of “instructions” given to cells early in life. According to this theory, BPH occurs because cells in one section of the gland follow these instructions and “reawaken” later in life. These “reawakened” cells then deliver signals to other cells in the gland, instructing them to grow or making them more sensitive to hormones that influence growth.

### 3.6 Symptoms

Many symptoms of BPH stem from obstruction of the urethra and gradual loss of bladder function, which results in incomplete emptying of the bladder. The symptoms of BPH vary, but the most common ones involve changes or problems with urination, such as

- a hesitant, interrupted, weak stream
- urgency and leaking or dribbling
- more frequent urination, especially at night

The size of the prostate does not always determine how severe the obstruction or the symptoms will be. Some men with greatly enlarged glands have little obstruction and few symptoms while others, whose glands are less enlarged, have more blockage and greater problems.

Sometimes a man may not know he has any obstruction until he suddenly finds himself unable to urinate at all. This condition, called acute urinary retention, may be triggered by taking over-the-counter cold or allergy medicines. Such medicines contain a decongestant drug, known as a sympathomimetic. A potential side effect of this drug may prevent the bladder opening from relaxing and allowing urine to empty. When partial obstruction is present, urinary retention also can be brought on by alcohol, cold temperatures, or a long period of immobility.

It is important to tell your doctor about urinary problems such as those described above. In eight out of 10 cases, these symptoms suggest BPH, but they also can signal other, more serious conditions that require prompt treatment. These conditions, including prostate cancer, can be ruled out only by a doctor's examination.

Severe BPH can cause serious problems over time. Urine retention and strain on the bladder can lead to urinary tract infections, bladder or kidney damage, bladder stones, and incontinence—the inability to control urination. If the bladder is permanently damaged, treatment for BPH may be ineffective. When BPH is found in its earlier stages, there is a lower risk of developing such complications.

### 3.7 Diagnosis

You may first notice symptoms of BPH yourself, or your doctor may find that your prostate is enlarged during a routine checkup. When BPH is suspected, you may be referred to a urologist, a doctor who specializes in problems of the urinary tract and the male reproductive system. Several tests help the doctor identify the problem and decide whether surgery is needed. The tests vary from patient to patient, but the following are the most common.

#### Digital Rectal Examination (DRE)

This examination is usually the first test done. The doctor inserts a gloved finger into the rectum and feels the part of the prostate next to the rectum. This examination gives the doctor

a general idea of the size and condition of the gland.

**Prostate-Specific Antigen (PSA) Blood Test**

To rule out cancer as a cause of urinary symptoms, your doctor may recommend a PSA blood test. PSA, a protein produced by prostate cells, is frequently present at elevated levels in the blood of men who have prostate cancer. The U.S. Food and Drug Administration (FDA) has approved a PSA test for use in conjunction with a digital rectal examination to help detect prostate cancer in men who are age 50 or older and for monitoring men with prostate cancer after treatment. However, much remains unknown about the interpretation of PSA levels, the test's ability to discriminate cancer from benign prostate conditions, and the best course of action following a finding of elevated PSA.

A fact sheet titled “The Prostate-Specific Antigen (PSA) Test: Questions and Answers” can be found on the National Cancer Institute website at “www.cancer.gov/cancertopics/factsheet/Detection/PSA”.

**Rectal Ultrasound and Prostate Biopsy**

If there is a suspicion of prostate cancer, your doctor may recommend a test with rectal ultrasound. In this procedure, a probe inserted in the rectum directs sound waves at the prostate. The echo patterns of the sound waves form an image of the prostate gland on a display screen. To determine whether an abnormal-looking area is indeed a tumor, the doctor can use the probe and the ultrasound images to guide a biopsy needle to the suspected tumor. The needle collects a few pieces of prostate tissue for examination with a microscope.

**Urine Flow Study**

Your doctor may ask you to urinate into a special device that measures how quickly the urine is flowing. A reduced flow often suggests BPH.

**Cystoscopy**

In this examination, the doctor inserts a small tube through the opening of the urethra in the penis. This procedure is done after a solution numbs the inside of the penis so all sensation is lost. The tube, called a cystoscope, contains a lens and a light system that help the doctor see

the inside of the urethra and the bladder. This test allows the doctor to determine the size of the gland and identify the location and degree of the obstruction.

### 3.8 Treatment

Men who have BPH with symptoms usually need some kind of treatment at some time. However, a number of researchers have questioned the need for early treatment when the gland is just mildly enlarged. The results of their studies indicate that early treatment may not be needed because the symptoms of BPH clear up without treatment in as many as one-third of all mild cases. Instead of immediate treatment, they suggest regular checkups to watch for early problems. If the condition begins to pose a danger to the patient's health or causes a major inconvenience to him, treatment is usually recommended.

Since BPH can cause urinary tract infections, a doctor will usually clear up any infection with antibiotics before treating the BPH itself. Although the need for treatment is not usually urgent, doctors generally advise going ahead with treatment once the problems become bothersome or present a health risk.

The following section describes the types of treatment that are most commonly used for BPH.

#### Drug Treatment

Over the years, researchers have tried to find a way to shrink or at least stop the growth of the prostate without using surgery. The FDA has approved six drugs to relieve common symptoms associated with an enlarged prostate.

Finasteride (Proscar), FDA-approved in 1992, and dutasteride (Avodart), FDA-approved in 2001, inhibit production of the hormone DHT, which is involved with prostate enlargement. The use of either of these drugs can either prevent progression of growth of the prostate or actually shrink the prostate in some men.

The FDA also approved the drugs terazosin (Hytrin) in 1993, doxazosin (Cardura) in 1995, tamsulosin (Flomax) in 1997, and alfuzosin (Uroxatral) in 2003 for the treatment of BPH. All four drugs act by relaxing the smooth muscle of the prostate and bladder neck to improve urine flow and to reduce bladder outlet obstruction. The four drugs belong to the class known as alpha blockers. Terazosin and doxazosin were developed first to treat high blood pressure.

Tamsulosin and alfuzosin were developed specifically to treat BPH.

The Medical Therapy of Prostatic Symptoms (MTOPS) Trial, supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), recently found that using finasteride and doxazosin together is more effective than using either drug alone to relieve symptoms and prevent BPH progression. The two-drug regimen reduced the risk of BPH progression by 67 percent, compared with 39 percent for doxazosin alone and 34 percent for finasteride alone.

**Minimally Invasive Therapy**

Because drug treatment is not effective in all cases, researchers in recent years have developed a number of procedures that relieve BPH symptoms but are less invasive than conventional surgery.

**Transurethral microwave procedures.** In 1996, the FDA approved a device that uses microwaves to heat and destroy excess prostate tissue. In the procedure called transurethral microwave thermotherapy (TUMT), the device sends computer-regulated microwaves through a catheter to heat selected portions of the prostate to at least 111 degrees Fahrenheit. A cooling system protects the urinary tract during the procedure.

The procedure takes about 1 hour and can be performed on an outpatient basis without general anesthesia. TUMT has not been reported to lead to erectile dysfunction or incontinence.

Although microwave therapy does not cure BPH, it reduces urinary frequency, urgency, straining, and intermittent flow. It does not correct the problem of incomplete emptying of the bladder. Ongoing research will determine any long-term effects of microwave therapy and who might benefit most from this therapy.

**Transurethral needle ablation.** Also in 1996, the FDA approved the minimally invasive transurethral needle ablation (TUNA) system for the treatment of BPH.

The TUNA system delivers low-level radiofrequency energy through twin needles to burn away a well-defined region of the enlarged prostate. Shields protect the urethra from heat damage. The TUNA system improves urine flow and relieves symptoms with fewer side

effects when compared with transurethral resection of the prostate (TURP). No incontinence or impotence has been observed.

**Water-induced thermotherapy.** This therapy uses heated water to destroy excess tissue in the prostate. A catheter containing multiple shafts is positioned in the urethra so that a treatment balloon rests in the middle of the prostate. A computer controls the temperature of the water, which flows into the balloon and heats the surrounding prostate tissue. The system focuses the heat in a precise region of the prostate. Surrounding tissues in the urethra and bladder are protected. Destroyed tissue either escapes with urine through the urethra or is reabsorbed by the body.

**High-intensity focused ultrasound.** The use of ultrasound waves to destroy prostate tissue is still undergoing clinical trials in the United States. The FDA has not yet approved high-intensity focused ultrasound.

**Surgical Treatment**

Most doctors recommend removal of the enlarged part of the prostate as the best long-term solution for patients with BPH. With surgery for BPH, only the enlarged tissue that is pressing against the urethra is removed; the rest of the inside tissue and the outside capsule are left intact. Surgery usually relieves the obstruction and incomplete emptying caused by BPH. The following section describes the types of surgery that are used.

**Transurethral surgery.** In this type of surgery, no external incision is needed. After giving anesthesia, the surgeon reaches the prostate by inserting an instrument through the urethra.

A procedure called transurethral resection of the prostate (TURP) is used for 90 percent of all prostate surgeries done for BPH. With TURP, an instrument called a resectoscope is inserted through the penis. The resectoscope, which is about 12 inches long and 1/2 inch in diameter, contains a light, valves for controlling irrigating fluid, and an electrical loop that cuts tissue and seals blood vessels.

During the 90-minute operation, the surgeon uses the resectoscope's wire loop to remove the obstructing tissue one piece at a time. The pieces of tissue are carried by the fluid into the bladder and then flushed out at the end of the operation.

Most doctors suggest using TURP whenever possible. Transurethral procedures are less traumatic than open forms of surgery and require a shorter recovery period. One possible side effect of TURP is retrograde, or backward, ejaculation. In this condition, semen flows backward into the bladder during climax instead of out the urethra.

Another surgical procedure is called transurethral incision of the prostate (TUIP). Instead of removing tissue, as with TURP, this procedure widens the urethra by making a few small cuts in the bladder neck, where the urethra joins the bladder, and in the prostate gland itself. Although some people believe that TUIP gives the same relief as TURP with less risk of side effects such as retrograde ejaculation, its advantages and long-term side effects have not been clearly established.

**Open surgery.** In the few cases when a transurethral procedure cannot be used, open surgery, which requires an external incision, may be used. Open surgery is often done when the gland is greatly enlarged, when there are complicating factors, or when the bladder has been damaged and needs to be repaired. The location of the enlargement within the gland and the patient's general health help the surgeon decide which of the three open procedures to use.

With all the open procedures, anesthesia is given and an incision is made. Once the surgeon reaches the prostate capsule, he or she scoops out the enlarged tissue from inside the gland.

**Laser surgery.** In March 1996, the FDA approved a surgical procedure that employs side-firing laser fibers and Nd: YAG lasers to vaporize obstructing prostate tissue. The doctor passes the laser fiber through the urethra into the prostate using a cystoscope and then delivers several bursts of energy lasting 30 to 60 seconds. The laser energy destroys prostate tissue and causes shrinkage. As with TURP, laser surgery requires anesthesia and a hospital stay. One advantage of laser surgery over TURP is that laser surgery causes little blood loss. Laser surgery also allows for a quicker recovery time. But laser surgery may not be effective on larger prostates. The long-term effectiveness of laser surgery is not known.

Newer procedures that use laser technology can be performed on an outpatient basis.

**Photoselective vaporization of the prostate (PVP).** PVP uses a high-energy laser to destroy prostate tissue and seal the treated area.

**Interstitial laser coagulation.** Unlike other laser procedures, interstitial laser coagulation places the tip of the fiberoptic probe directly into the prostate tissue to destroy it.

# Chapter 4:

## (HIROFILOS I ) An Intelligent System For Prostate Diseases Diagnosis

## 4.1 Introduction

Prostate gland diseases, including cancer are estimated to be one of the leading cause of male death worldwide and its management is based on guidelines regarding diagnosis, evaluation, treatment and continuing care. Prostate cancer is the most common noncutaneous cancer among males [1]. The diagnosis and treatment of prostate cancer continue to evolve. With the development of prostate-specific antigen (PSA) screening, more men are identified earlier as having prostate cancer. While prostate cancer can be a slow-growing cancer, thousands of men die of the disease each year. Benign prostatic hyperplasia (BPH) is a noncancerous enlargement of the prostate gland that may restrict the flow of urine from the bladder. BPH involves both the stromal and epithelial elements of the prostate arising in the periurethral and transition zones of the gland; the condition is considered a normal part of the aging process in men and is hormonally dependent on testosterone production. An estimated 50% of men demonstrate histopathologic BPH by age 60 years. This number increases to 90% by age 85 years; thus, increasing gland size is considered a normal part of the aging process. Acute prostatitis (AP) presents as an acute urinary tract infection in men. It is much less common than chronic prostatitis (CP)but is easier to identify because of its more uniform clinical presentation. Chronic prostatitis, is poorly understood partly because of its uncertain etiology and lack of clearly distinguishing clinical features. Acute prostatitis is usually associated with predisposing risk factors, including bladder outlet obstruction secondary to benign prostatic hyperplasia (BPH) [1].

Different approaches according to medical as well as psychosocial characteristics of patients are usually followed for diagnosis of the previous diseases. Like any chronic disease, prostate is complex to manage.

Traditionally, an intelligent system that helps clinicians to diagnose and treat diseases is used to identify a patient-specific clinical situation on the basis of key elements of clinical and laboratory examinations and consequently usually refine a theoretical treatment strategy, a priori established in the guideline for the corresponding clinical situation, by the specific therapeutic history of the patient [2]. Depending on the patient's data, it models patient scenarios which drive decision making and are used to synchronize the management of a patient with guideline recommendations. The so-

called guideline-based treatment choice can be considered under the main difference between management of acute and chronic disease that is the time. Guideline Dependence introduces a computer-assisted intelligent Decision Support Systems (DSSs), based on technologies that provide to the patient “most likely” treatment scenario [2], [3], [4]. So, the creation of an expert system to assist non-expert doctors in making an initial diagnosis would is very desirable [5], [6], [7]. Most of the systems that have been proposed and used focus on PC diagnosis. Additionally as it is known, real world medical knowledge is often characterized by inaccuracy. Medical terms do not usually have a clear-cut interpretation. Fuzzy logic makes it possible to define inexact medical entities via fuzzy sets. During last decade, a number of fuzzy techniques have appeared which, have been extensively applied to medical systems [8], [9]. One of the reasons is that fuzzy logic provides reasoning methods for approximate inference [8], that is inference with inaccurate (or fuzzy) terms. In this paper, we present a fuzzy expert system for the diagnosis and treatment of prostate diseases (called HIROFILOS from the ancient Greek doctor who first described and named prostate gland). HIROFILOS primarily aims to help in the diagnosis and treatment of prostate diseases effectively under the consideration of LUTS. Also, it can be used by medical students for training purposes on prostate disease management and introduce a computer-assisted environment that is able to synthesise patient specific information with treatment guidelines, perform complex evaluations, and present the results to health professionals quickly.

### 4.1.2 Topics of Research

Developing program That Use (ML) As A Tool For Help TO Diagnosis Prostate Gland Disease.

### 4.1.3 Purpose of Research

- ✓ Improves personal efficiency
- ✓ Expedites problem solving (speed up the progress of problems solving in an organization)
- ✓ Increases organizational control.
- ✓ Supporting clinical coding and documentation, authorization of procedures, and referrals.

- ✓ "Managing clinical complexity and details: Keeping patients on research and chemotherapy protocols; tracking orders, referrals follow-up and preventive care.
- ✓ "Cost control: Monitoring medication orders; avoiding duplicate or unnecessary tests.
- ✓ "Decision support: Supporting clinical diagnosis and treatment plan processes; and promoting use of best practices, condition-specific guidelines, and population-based management

### 4.1.4 Research Plane

My research interests lie in information retrieval, data mining and machine learning, document analysis, digital library, biomedical and health informatics, natural language processing, software engineering.
In particular, my research goal is to create tools and algorithms for Help to Diagnosis Prostate Gland Disease

### 4.1.5 Expectations:

I hope to be able to develop a passive sampling device to monitor and analyze Diagnosis Prostate Gland Disease.

## 4.2 Medical Knowledge Modeling

Appropriate diagnosis of AP, CP, BPH and AC requires urology doctors with long experience in Urology. One of the problems is that there is no a widely accepted approach yet. Therefore, except from the fact that we had a number of interviews with an expert in the field, we also used patient records and bibliographical sources. Our approach to knowledge modeling included three steps. First, we constructed a model of the basic diagnosis and treatment process. We relied on the expert and the literature at this step (Fig. 1). Then, we specified the parameters that played a role in each entity of the process model. At this step, we relied on the expert and the patient records. Finally, we determined the fuzzy models for the values of the resulted linguistic variables. We had, however, to iterate a number of times on this last step to tune the model (Fig. 2).

### 4.2.1 Input-output variables

Based on our expert, we specified a set of parameters that play a role for each of the entities in the process model that represent patient data (Fig. 1). Finally, we resulted in the following parameters for each entity in the process model. According to the model, we distinguish between *input*, *intermediate* and *final* parameters at each sub process.

*Input parameters:* (a) bladder not empty sensation, (b) less than 2 hours urination, (c) urination stopping, (d) difficulty to prostpone urination, (e) night urination (1 to 5), (f) quality of life, (g) fever, (i) hematuria, (j) hemospermia, (k) painful ejaculation, (l) fever, (m) chills, (n) perineal pain, (o) bone pain, (p) pyuria, (q) age.

*Intermediate output parameters:* (a) LUTS (yes, no), (b) DRE (normal, big, painful, stony).

*Intermediate input parameters:* (a) LUTS (yes, no), (b) PSA (normal, middle, high).

*Final output parameters:* (a) Prostate disease (AP, CP, BPH, PC) (b) Biopsy

*Final treatment parameters:* Final treatment according to current Prostate disease (a) simple follow up (b) medication (antibiotics, etc) and (c) surgery (open, urethral, laser, microwaves)

### 4.2.2 LUTS diagnosis

The *knowledge base* of the expert system includes *production rules*, which are symbolic (if-then) rules with Boolean or crisp variables (e.g. age, smoke, cholesterol, etc). The variables of the conditions (or antecedents) of a rule are inputs and the variable of its conclusion (or consequent) an output of the system. To represent the process model, we organized production rules in three groups: *LUTS classification rules*, *prostate diagnostic rules* and *treatment rules* inspired form model presented in Fig. 1. The current patient data are stored in the Patient Database, as *facts*. Each time that the reasoning process requires a parameter value, it gets it from the database or the user. In a pure interactive mode, it could be given only by the user.

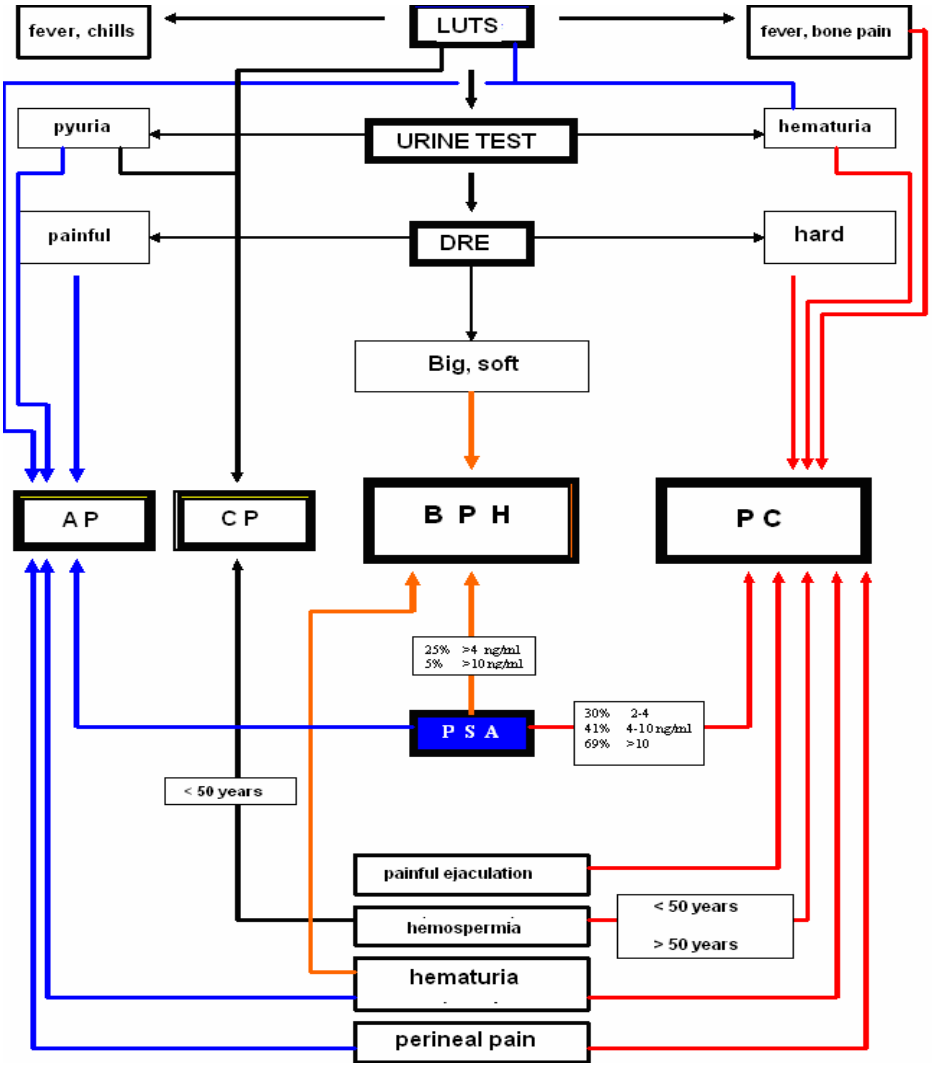



**Fig.1:** Prostate Diagnosis Process Model

Fig.3 presents how the rule groups and the facts or user are used or participates during the reasoning process to simulate the diagnosis process.

**Table 1.** Lower Urinary Tract Symptoms classification rules (partial)

| **Stop urination** | **Weak urination** | **Night Urination** | **…** | **LUTS** |
|---|---|---|---|---|
| Less than 1 | Less than 1 | 1 | | No |
| Less than half | Less than half | 1 | … | No |
| About half | Less than half | 1 to 3 | | Yes |
| More than half | Less than half | 1 to 3 | | yes |
| Always | About ahalf | 1 to 3 | … | Yes |
| … | … | 1 to 3 | | yes |

### 4.2.3 Prostate disease diagnosis

To represent the process model, we organized production rules in two groups: *LUTS classification Rules* and *Prostate Diagnostic Rules*. *LUTS rules* classify the current patient data to a specific patient model according to the calculated LUTS Factor. These values are stored in the patient database. A sample of *LUTS rules* can be seen in Table 1.

**Table 2.** Prostate diseases diagnostic rules (partial)

| **INTERMEDIATE INPUT** | | | **DIAGNOSTIC RULES** | | | |
|---|---|---|---|---|---|---|
| **LUTS** | **DRE** | **PSA** | **AP** | **CP** | **BPH** | **PCA** |
| Yes | Hard | High | No | No | No | Yes |
| Yes | Hard | High | Yes | No | No | Yes |
| Yes | Painful | Middle | Yes | Yes | Yes | No |
| Yes | Painful | Middle | Yes | Yes | No | No |
| | … | … | | | | |
| No | No | Normal | No | No | No | No |


For each patient dataset that is stored in the Patient Database, *Prostate diagnosis Rules* decide to ask for the parameter PSA values in order to give to the user the final diagnosis. Each time that the reasoning process requires a value, it gets it from the database or from user interaction. A sample of *Prostate diagnosis rules* can be seen in Table 1. Finally there are a small number of *Treatment* rules, which according to the resulted disease provide the appropriate treatment strategy.

ου του προστάτη.

**A**


**B**

**Εικόνα 08.1.1**: HIROFILOS interface (a) and system functions (b)

### 4.3 HIROFILOS architecture

The developed fuzzy expert system has the structure of Fig. 2, which is similar to the typical structure of such systems [8], [9]. The *knowledge base* of the expert system includes *fuzzy rules*, which are symbolic (if-then) rules with linguistic variables (e.g.age). Linguistic variables take linguistic values (e.g., middleaged, old). Each linguistic value is represented by a *fuzzy set*: a range of crisp (i.e. non-linguistic) values with different degrees of membership to the set. The degrees are specified via a *membership function*. The variables of the conditions (or antecedents) of a rule are inputs and the variable of its conclusion (or consequent) an output of the system.

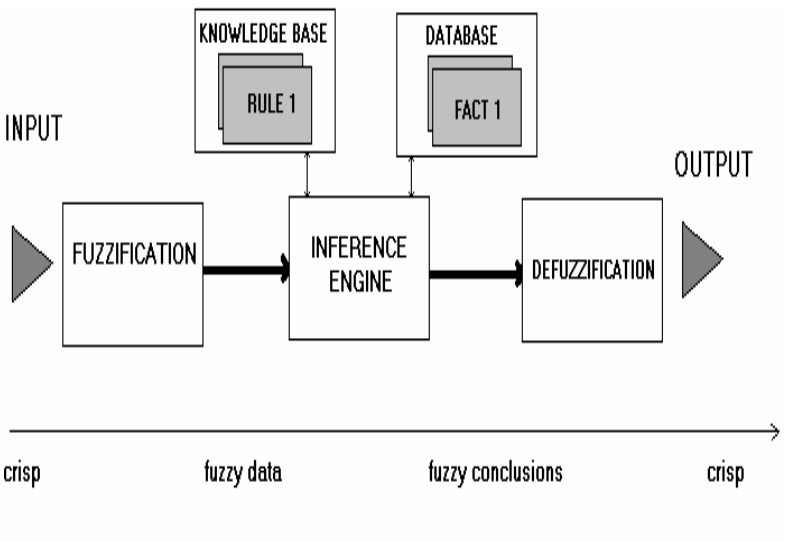



**Fig. 2. The general structure of HIROFILOS**

Reasoning in such a system includes three stages: fuzzification, inference, defuzzification. In *fuzzification*, the crisp input values (from the fact database) are converted to membership degrees, by applying the corresponding membership functions, that become the truth degrees of the corresponding conditions of the fuzzy rules. In the *inference* stage, first, the degrees of the conditions of the fuzzy rules are combined to produce the degrees of truth of the conclusions. The MIN method is used here. According to that, the degree of truth of a conclusion is the minimum of the degrees of the conditions of the corresponding rule (AND fuzzy operation) and its membership function is clipped off at a height corresponding to that minimum. Afterwards, all the degrees assigned to same conclusions (i.e. rule outputs) are combined into a single degree using the MAX method. According to that, the combined output degree of truth is the maximum of the degrees (OR fuzzy operation) and its membership function is clipped off at a height corresponding to that maximum. Finally, the clipped off membership functions of all outputs are aggregated to form the combined fuzzy output. In *defuzzification*, the fuzzy output is converted to a crisp value. Here, the well-known centroid method is used. According to that method, the crisp output value is the x-coordinate value of the centre of gravity of the aggregate membership function [8].

To represent the process model, we organized fuzzy rules in three groups: *classification rules*, *diagnostic rules* and *treatment rules*. The current patient data are stored in the Database, as *facts*. Each time that the reasoning process requires a value, it gets it from the database. In an interactive mode, it could be given by the user. Fig.3

presents how the rule groups and the facts/user are used/participates during the reasoning process to simulate the diagnosis process.

### 4.4 Implementation Issues

The user interface has been developed with Macromedia Flash 8.0, and the fuzzy expert system has been developed in FuzzyCLIPS 6.1b Expert System Shell. Finally, about 84 rules have been constructed. Patient data in the Database are organized by using FuzzyCLIPS templates. For example, the following rules are presented.

Next rule asks the user to input parameters about LUTS:

```
(defrule Questions_LUTS  "ask-question"
(initial-fact)
=>
(printout  t "Question About LUTS "  t)
…
(bind  ?empty  (ask-question " Do you feel your bladder is not quite empty after you have been to pass urine (yes/no)?" yes no) )
(assert (empty ?empty))
```

Next group of rules gives the intermediate diagnosis of LUTS:

```
(defrule_5
(declare(salience 40))
(or(pass_urine yes)
(flow yes)
(trickles yes)
(thinner yes)
(empty yes)
(get_up yes)
(daytime yes)
(straight yes)
(mean yes))
=>
(assert (A  yes)))
…
```

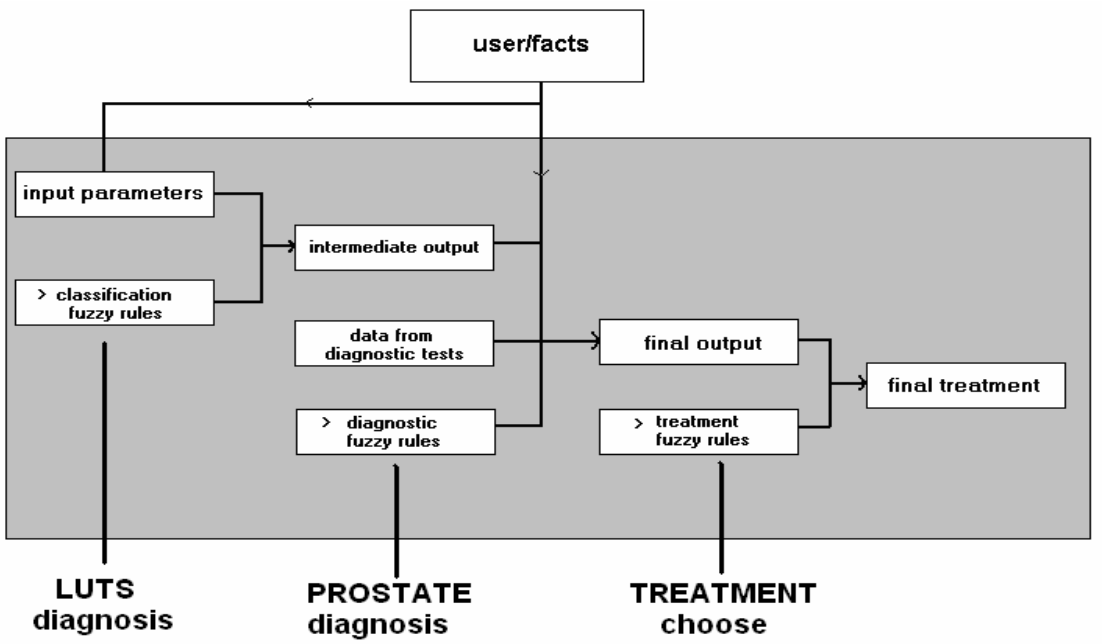



**Fig. 3.** The reasoning flow in HIROFILOS

(defrule print_a
(A yes)
(end yes)
=>
(printout t "*** **you have severe symptoms and should consult your own doctor** ** You may need an examination, and possibly a blood test. Your doctor may consider referring you for an operation to remove the prostate gland, or may consider putting you on a course of tablets *" crlf))

Next rule inserts as final diagnosis Prostate Cancer,
**Rule 46: If patient LUTS is yes and haemospermia is yes and painful_ejaculationl is yes or fever is yes then disease is Prostate Cancer.**

has been implemented in FuzzyCLIPS as follows:

(defrule _46
*(declare(salience 20)*
(and(luts haematuria)
(luts haemo_spermia )

(luts painful_ejaculation)

(luts fever))

=>

(assert(PCA (value yes)))

To implement reasoning flow, different priorities have been used for different rule groups (named *salience(?))*.


Image 4.1 : Patient data entry

### 4.5 Experimental Results

We used HIROFILOS for a number of 105 patient records from the Hospital Database with different types of prostate diseases. The corresponding treatment results were compared to the results of our expert doctor. To evaluate HIROFILOS, we used three metrics, commonly used for this purpose: accuracy, sensitivity and specificity (abbreviated as Acc, Sen and Spec respectively), defined as follows:

$Acc=(a + d)/(a + b + c + d)$,

$Sen = a/(a + b)$,

*Spec = d/(c + d)*

where, *a* is the number of positive cases correctly classified, *b* is the number of positive cases that are misclassified, *d* is the number of negative cases correctly classified and *c* is the number of negative cases that are misclassified. By 'positive' we mean that a case belongs to the group of the corresponding initial treatment and by negative that it doesn't. The evaluation results are presented in Table 3 and show an acceptable performance.

**Table 3.** Evaluation results for initial diagnosis of prostate disease patients

| Metrics | EXPERT | HIROFILOS |
|---|---|---|
| **ACCURACY** | 0.95 | 0.76 |
| **SENSITIVITY** | 0.98 | 0.79 |
| **SPECIFICITY** | 0.99 | 0.75 |

### 4.6 Conclusions

In this paper, we present the design, implementation and evaluation of HIROFILOS, a fuzzy expert system that deals with diagnosis and treatment of prostate diseases except prostate cancer that is the usual diagnosis of most similar approaches in the same medical field [2], [3], [6]. The diagnosis process was modeled based on expert's knowledge and existing literature. Linguistic variables were specified based again on expert's knowledge and the statistical analysis of the records of 105 patients from a hospital database. Linguistic values were determined by the help of expert, the statistical analysis and bibliographical sources. Experimental results showed that HIROFILOS did quite better than non-expert urologists, but worse than the expert. A possible reason for that may be the determination of the values (fuzzy sets) of the linguistic variables and their membership functions. Better choices may give better results. One the other hand, use of alternative or more advanced representation methods, like hybrid ones [6], [10], [11] may give better results.

# Chapter 5:

# Using Machine Learning Techniques to improve the behaviour of a medical decision support system for prostate diseases

## Machine Learning with Weka

### 5.1 Description


The Weka logo. Weka is a bird endemic to New Zealand.

The Weka workbench[1] contains a collection of visualization tools and algorithms for data analysis and predictive modeling, together with graphical user interfaces for easy access to this functionality. The original non-Java version of Weka was a TCL/TK front-end to (mostly third-party) modeling algorithms implemented in other programming languages, plus data preprocessing utilities in C, and a Makefile-based system for running machine learning experiments. This original version was primarily designed as a tool for analyzing data from agricultural domains,[2][3] but the more recent fully Java-based version (Weka 3), for which development started in 1997, is now used in many different application areas, in particular for educational purposes and research. The main strengths of Weka are that it:

- is freely available under the GNU General Public License,
- is very portable because it is fully implemented in the Java programming language and thus runs on almost any modern computing platform,
- contains a comprehensive collection of data preprocessing and modeling techniques, and
- Is easy to use by a novice due to the graphical user interfaces it contains.

**Weka** (Waikato Environment for Knowledge Analysis) is a popular suite of machine learning software written in Java, developed at the University of Waikato, New Zealand. WEKA is free software available under the GNU General Public License.

### 5.2 Working with WEKA

Weka supports several standard data mining tasks, more specifically, data preprocessing, clustering, classification, regression, visualization, and feature selection. All of Weka's techniques are predicated on the assumption that the data is available as a single flat file or

relation, where each data point is described by a fixed number of attributes (normally, numeric or nominal attributes, but some other attribute types are also supported). Weka provides access to SQL databases using Java Database Connectivity and can process the result returned by a database query. It is not capable of multi-relational data mining, but there is separate software for converting a collection of linked database tables into a single table that is suitable for processing using Weka[4]. Another important area that is currently not covered by the algorithms included in the Weka distribution is sequence modeling.

Weka's main user interface is the *Explorer*, but essentially the same functionality can be accessed through the component-based *Knowledge Flow* interface and from the command line. There is also the *Experimenter*, which allows the systematic comparison of the predictive performance of Weka's machine learning algorithms on a collection of datasets.

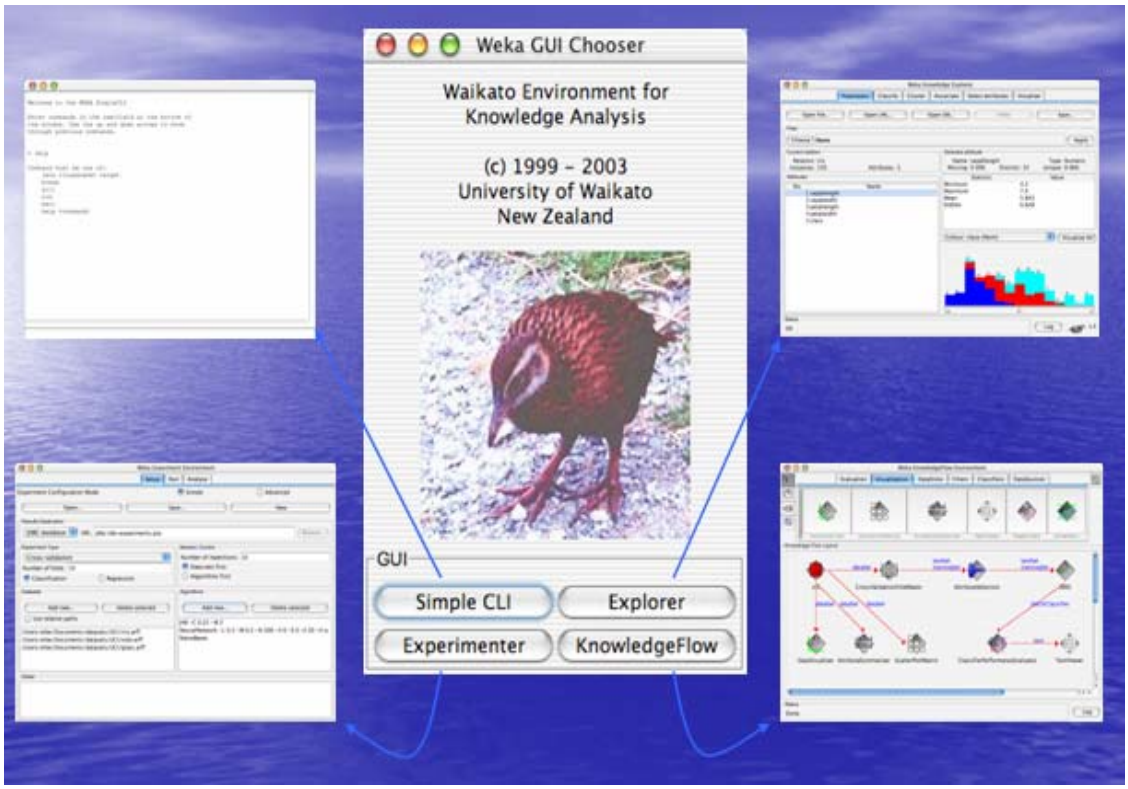



**Image 4.1 : WEKA enviroment**

The Explorer interface has several panels that give access to the main components of the workbench. The Preprocess panel has facilities for importing data from a database, a CSV file, etc., and for preprocessing this data using a so-called filtering algorithm. These filters can be used to transform the data (e.g., turning numeric attributes into discrete ones) and

make it possible to delete instances and attributes according to specific criteria. The Classify panel enables the user to apply classification and regression algorithms (indiscriminately called classifiers in Weka) to the resulting dataset, to estimate the accuracy of the resulting predictive model, and to visualize erroneous predictions, ROC curves, etc., or the model itself (if the model is amenable to visualization like, e.g., a decision tree). The Associate panel provides access to association rule learners that attempt to identify all important interrelationships between attributes in the data. The Cluster panel gives access to the clustering techniques in Weka, e.g., the simple k-means algorithm. There is also an implementation of the expectation maximization algorithm for learning a mixture of normal distributions. The next panel, Select attributes provides algorithms for identifying the most predictive attributes in a dataset. The last panel, Visualize, shows a scatter plot matrix, where individual scatter plots can be selected and enlarged, and analyzed further using various selection operators.

## 5.3. Introduction

In recent years artificial intelligence (AI) techniques using data from patient electronic health records or implementing clinical practice guidelines have been used in many information systems related to the medical field. As computerized health-care support systems are rapidly

becoming more knowledge intensive, the need for representation of medical knowledge in a form that enables effective reasoning is growing.

Prostate gland diseases, including cancer, are estimated to be one of the leading cause of male deaths worldwide. Its management is based on guidelines regarding diagnosis, evaluation, treatment and continuing care. Prostate cancer is the most common noncutaneous cancer among males [1]. Diagnosis and treatment of prostate cancer continue to evolve. With the development of prostate-specific antigen (PSA) screening, more men are early identified as having prostate cancer. While prostate cancer can be a slow-growing cancer, thousands of men die of the disease each year. Benign prostatic hyperplasia (BPH) is a noncancerous enlargement of the prostate gland that may restrict the flow of urine from the bladder. BPH involves both the stromal and epithelial elements of the prostate arising in the periurethral and transition zones of the gland; the condition is considered a normal part of the aging process in men and is hormonally dependent on testosterone production. An estimated 50% of men demonstrate histopathologic BPH by the age of 60. This number increases to 90% by the age of 85; thus, increasing gland size is considered a normal part of the aging process. Acute prostatitis (AP) is presented as an acute urinary tract infection in men. It is much less common than chronic prostatitis (CP), but is easier to identify, because of its more uniform clinical presentation. AP is usually associated with predisposing risk factors, including bladder outlet obstruction secondary to benign prostatic hyperplasia (BPH) [2].

Different approaches according to medical as well as psychosocial characteristics of patients are usually followed for diagnosis of the above diseases. Like any chronic disease, prostate is complex to manage. Traditionally, an intelligent system that helps clinicians to diagnose and treat diseases is used to identify a patient-specific clinical situation on the basis of key elements of clinical and laboratory examinations and consequently refine a theoretical treatment strategy, a priori established in the guidelines for the corresponding clinical situation, by the specific therapeutic history of the patient [1]. Depending on the patient's data, it models patient scenarios which drive decision making and are used to synchronize the management of a patient with guideline recommendations. Guideline dependence leads to intelligent decision support systems, based on technologies that provide the “most likely” treatment scenario for the patient [2], [3], [4]. So, the creation of an information system to assist non-expert doctors in making an initial diagnosis is always desirable [5], [6], [7]. Most of the systems that have been proposed and used focus on CP diagnosis , [5], [6], [7], [8].

In order to develop a successful decision-support and knowledge management system, appropriate medical knowledge representation approaches should be employed. A successful information system has to include efficient representations, technologies, and tools that integrate all the important elements that physicians work with: electronic health records, clinical practice guidelines, etc. As it is known, real world medical knowledge is often characterized by inaccuracy. Medical terms do not usually have a clear-cut interpretation. Fuzzy logic makes it possible to define inexact medical knowledge via fuzzy sets. During last decade, a number of fuzzy techniques have appeared which, have been extensively applied to medical systems [8], [10], [12]. One of the reasons is that fuzzy logic provides reasoning methods for approximate inference, that is inference with inaccurate (or fuzzy) terms. In this paper, we present an intelligent information system, called HIROFILOS-II, that primarily aims to help in effective diagnosis and treatment of prostate diseases taking into consideration the Lower Urinary Tract Symptoms (LUTS) [1]. It introduces a computer-assisted environment that is able to synthesise patient information with treatment guidelines, perform complex evaluations, and present the results to health professionals quickly.

Its previous version, HIROFILOS-I, was developed based on knowledge elicited from urology experts and bibliographic research ratified with statistical results from clinical practice [9]. Although preliminary experimental results demonstrated acceptable performance for the most common prostate diseases, the system has been improved by using machine learning techniques to extract knowledge, in if-then rule form, from empirical data (i.e.patient records). Thus, it now covers all prostate diseases, as well as CP, which is still poorly understood partly because of its uncertain etiology, bu**t mainly because of lack of clearly distinguishing clinical features.**

The structure of the paper is as follows. Section 2 presents the medical knowledge modelling. In Section 3, the system architecture of HERIFOLOS-II is described. In Section 4 implementation issued are presented. Section 5 contains evaluation results. Finally Section 6 concludes.

### 5.4. Medical Knowledge Modelling

Appropriate diagnosis of AP, CP, BPH and AC requires urology doctors with long experience in Urology. One of the problems is that there is not a widely acceptable approach

yet. Therefore, except from the fact that we had a number of interviews with an expert in the field, we also used patient records and bibliographical sources [1].

### 5.4.1 Input-output variables

Based on our expert, we specified a set of parameters that play a role in the diagnosis process and its subprocesses (see Fig. 1). Finally, we resulted in the following parameters, which are distinguished in *input*, *intermediate* and *final* parameters at each sub process.

- *Input parameters:* (a) bladder not empty sensation, (b) less than 2 hours urination, (c) urination stopping, (d) difficulty to prostpone urination, (e) night urination (1 to 5), (f) quality of life, (g) fever, (i) hematuria, (j) hemospermia, (k) painful ejaculation, (l) fever, (m) chills, (n) perineal pain, (o) bone pain, (p) pyuria, (q) age.
- *Intermediate output parameters:* (a) LUTS (yes, no), (b) DRE (normal, big, painful, stony).
- *Intermediate input parameters:* (a) LUTS (yes, no), (b) PSA (normal, medium, high).
- *Final output parameters:* (a) Prostate disease (AP, CP, BPH, PC) (b) Biopsy
- *Final treatment parameters:* Final treatment according to current Prostate disease (a) simple follow up (b) medication (antibiotics, etc) and (c) surgery (open, urethral, laser, microwaves).

### 5.4.2 Diagnosis Process Model

Based on our expert and the European Association Guidelines, we constructed a model for the prostate diagnosis process, depicted in Fig. 1. According to that model, first the expert defines the existence of Lower Urinary Track Symptoms (LUTS) [1]. If the diagnosis is positive, the performed clinical examination (for pain, fever etc), the results of special urine tests (for pyouria, hematuria, etc), as well as blood tests (for PSA levels) and finally the Direct Ring Examination of prostate (for prostate gland characterization), provide doctors additional information that combined with patients' demographic data (age, etc) helps in concluding about the possible prostate disease and the appropriate therapeutic strategy [1, 9].

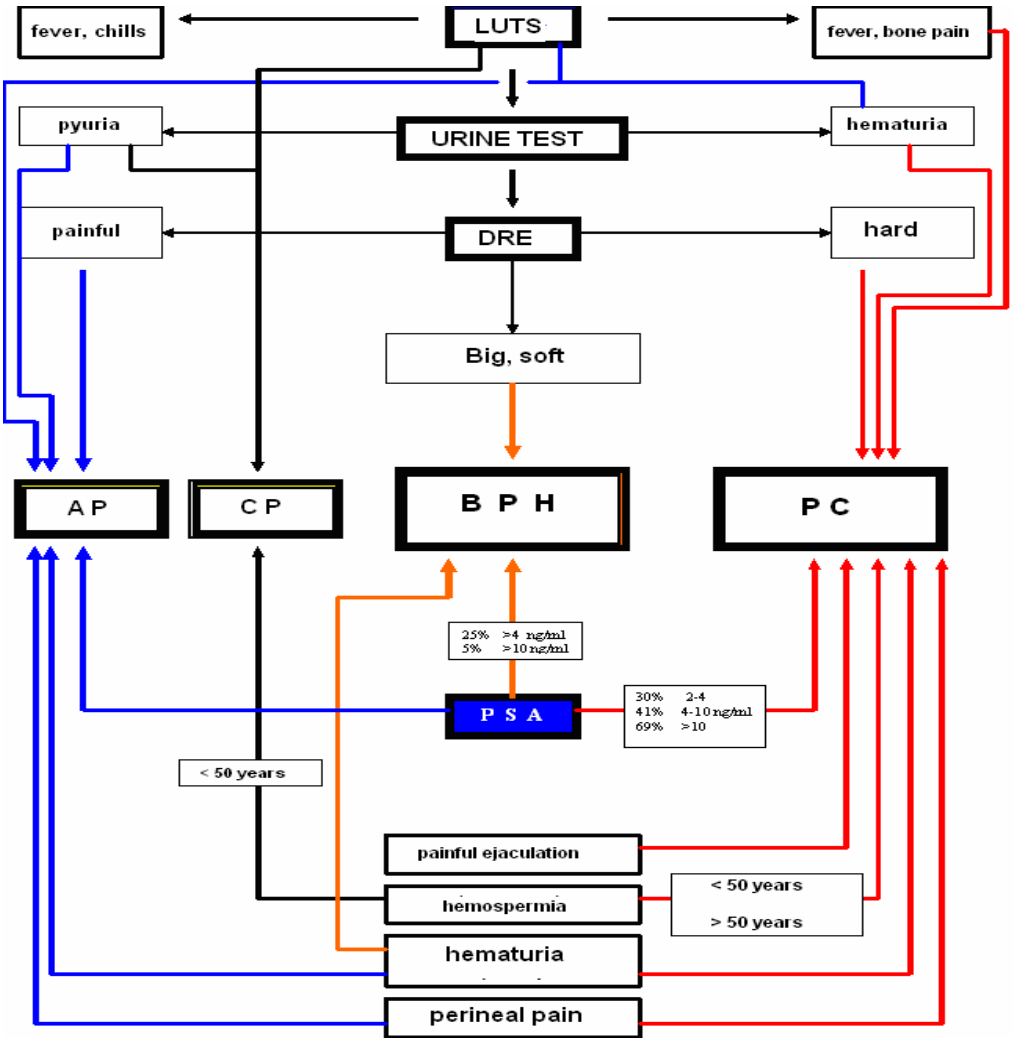



Fig. 1: Prostate Diagnosis Process Model

### 5.4.3 Prostate disease diagnosis

To represent the process model, we organized prostate related rules in three groups: *LUTS classification module* (crisp rules), *Prostate Diagnostic module* (fuzzy rules) and *Prostate Treatment module* (fuzzy rules). *LUTS module* classifies the current patient data to a specific patient model according to the calculated LUTS Factor. These values are stored in the patient health record database. A sample of *LUTS rules* can be seen in Table 1.

For each patient record that is stored in the Patient Database, *Prostate diagnosis module* decides to ask for the parameter PSA values in order to give to the user the final diagnosis. Each time that the reasoning process requires a value, it gets it from the database or from user

interaction. A sample of *Prostate disease diagnosis rules* can be seen in Table 2. Finally there are a small number of *Prostate treatment* rules, which according to the resulted disease provide the appropriate treatment strategy.

**Table 1.** Lower Urinary Tract Symptoms classification rules (partial)

| **Stop urination** | **Weak urination** | **Night Urination** | **…** | **LUTS** |
|---|---|---|---|---|
| Less than 1 | Less than 1 | 1 | | No |
| Less than half | Less than half | 1 | … | No |
| About half | Less than half | 1 to 3 | | Yes |
| More than half | Less than half | 1 to 3 | | yes |
| Always | About ahalf | 1 to 3 | … | Yes |
| … | … | 1 to 3 | | yes |

**Table 2.** Prostate diseases diagnostic rules (partial)

| **INTERMEDIATE INPUT** | **DIAGNOSTIC** |
|---|---|

| | | | RULES | | | |
|---|---|---|---|---|---|---|
| **LUTS** | **DRE** | **PSA** | **AP** | **CP** | **BPH** | **PCA** |
| Yes | Hard | High | No | No | No | Yes |
| Yes | Hard | High | Yes | No | No | Yes |
| Yes | Painful | Middle | Yes | Yes | Yes | No |
| Yes | Painful | Middle | Yes | Yes | No | No |
| | … | … | | | | |
| No | No | Normal | No | No | No | No |

### 5.5. HIROFILOS-II Architecture and Design

The developed intelligent system for all prostate diseases has the structure of Fig. 2. The core of the system is a fuzzy expert system [8], [11] augmented by an off-line machine learning component. The *knowledge base* of the expert system includes *crisp or fuzzy rules*, distributed in groups. Fuzzy rules are symbolic (if-then) rules with linguistic variables (e.g. age), which take linguistic values (e.g., middleaged, old). Each linguistic value is represented by a *fuzzy set*: a range of crisp (i.e. non-linguistic) values with different degrees of membership to the set. The degrees are specified via a *membership function* [10, 11]. The variables of the conditions (or antecedents) of a rule represent inputs and the variable of its conclusion (or consequent) an output of the system.

Reasoning in such a system includes three stages: fuzzification, inference, defuzzification. In *fuzzification*, the crisp input values (from the fact database) are converted to membership degrees, by applying the corresponding membership functions, that become the truth degrees of the corresponding conditions of the fuzzy rules. In the *inference* stage, first, the degrees of the conditions of the fuzzy rules are combined to produce the degrees of truth of the conclusions. In *defuzzification*, the fuzzy output is converted to a crisp value. Here, the well-known centroid method is used. According to that method, the crisp output value is the x-coordinate value of the center of gravity of the aggregate membership function [11].

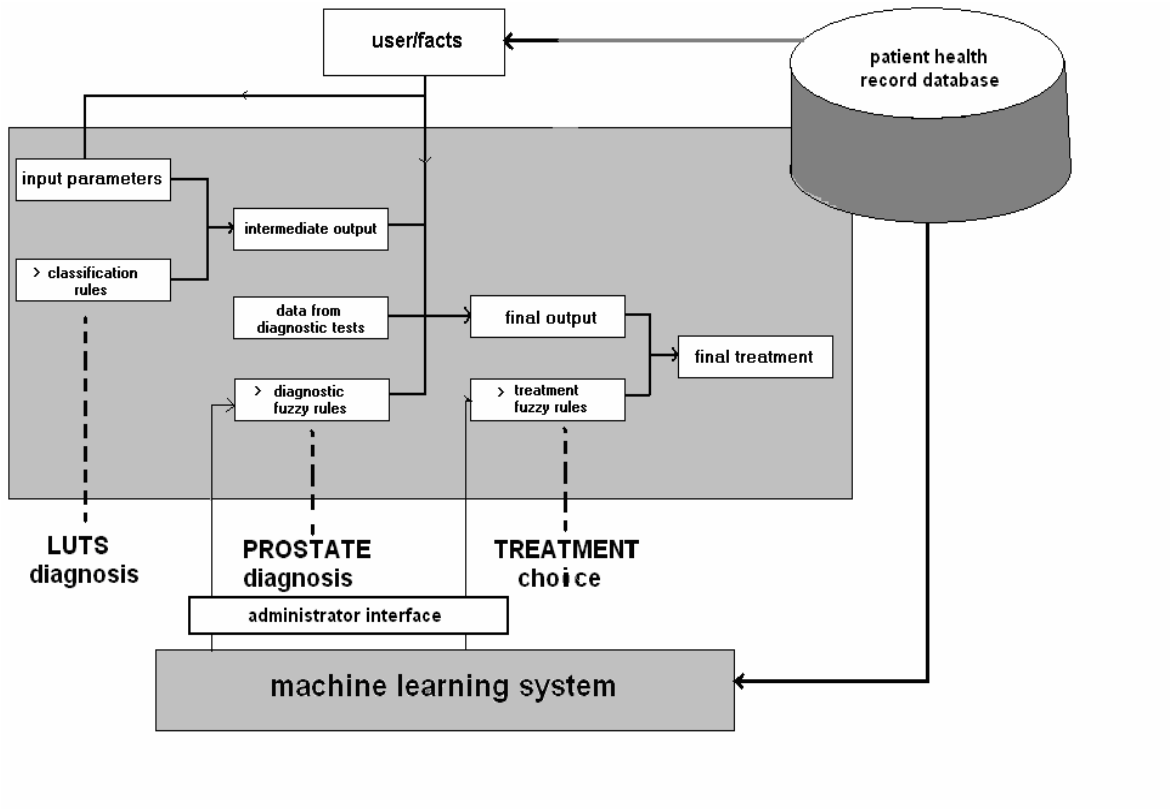



**Fig. 2.** The general structure of and reasoning flow in HIROFILOS-II

To represent the process model, we organized rules in three groups: *classification rules*, *diagnostic rules* and *treatment rules*. From those, the first contains crisp rules, whereas the other two fuzzy rules. The current patient data are stored in the System Database, as *facts*. Each time the reasoning process requires a value, it gets it from the database. In an interactive mode, it could be given by the user. Fig.2 presents how the rule groups and the facts/user are used/participates during the reasoning process to simulate the diagnosis process.

The machine learning system includes some of the well known data mining tools (such as those included in WEKA) as off-line developers, to extract rules from the patient records. It has been initially used for constructing the expert system, but it will be mainly used to periodically evolve the fuzzy expert systems, based on new patient cases stored in the database. Health record data was used for induction, and the exported/constructed rules have been transformed into the fuzzy knowledge base by the administrator of the system and finally integrated with the expert knowledge (Fig. 2).

## 5.6. Implementation Issues

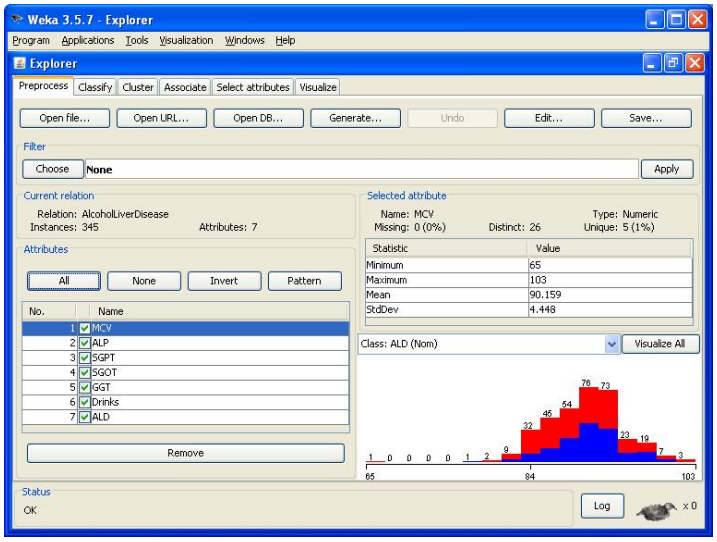



Image 5.1 WEKA after file load

The user interface of the system has been developed with C#.NET v2003, in order to be used as a web-based application on a hospital web server, and the fuzzy expert system has been developed in FuzzyCLIPS 6.1b Expert System Shell. We used WEKA (more specifically, algorithm J48) for tree-form rule extraction to produce an initial number of rules. Then rules were modified based on expert advice. Finally, about 84 rules have been constructed. To implement reasoning flow, we implemented each rule group as a *module* in CLIPS. Patient health records from the Database are recognized by using FuzzyCLIPS *templates*. Following are some example rules:

Next rule asks the user to input parameters about LUTS:

```
(defrule Questions_LUTS  "ask-question"
(initial-fact)
=>
(printout  t "Question About LUTS "  t)
…
(bind  ?empty  (ask-question " Do you feel your bladder is not quite empty after you have been to pass urine (yes/no)?" yes no) )
(assert (empty ?empty))
```

Next rule gives the intermediate diagnosis of LUTS:

```
(defrule_5
(declare(salience 40))
(or(pass_urine yes)
(flow yes)
(trickles yes)
(thinner yes)
(empty yes)
(get_up yes)
(daytime yes)
(straight yes)
(mean yes))
=>
(assert (LUTS yes)))
(defrule print_LUTS
(LUTS  yes)
(end yes)
=>
(printout  t "*** you have severe LUT symptoms and should consult your own doctor ** You may need an examination, and possibly a blood test. Your doctor may consider referring you for an operation to remove the prostate gland, or may consider putting you on a course of tablets *" crlf))
```

Next rule is a fuzzy rule that concerns prostate cancer final diagnosis:

```
 (defrule R_4
 (declare (CF 0.1))
 (and(fever no)(GRN enlarged)(PSA high))
 =>
  (assert (PCA (value yes))
)
```

## 5.7. Experimental results

HIROFILOS-I was tested on a number of 200 patient records from a Hospital Database with different types of prostate diseases. Data that was the input to the system, was taken from electronic health records that were recorded in the hospital by the doctors. The type of data that is usually stored in these records, are numeric as well linguistic. To evaluate HIROFILOS-II, the same test set has been used and three statistical metrics were calculated for this purpose: accuracy, sensitivity and specificity. The gold standard that used was the 90% for all metrics as sensitivity and specificity, for all the classes in this problem. The final corresponding diagnosis results were compared to the results of a specialized urology doctor for prostate cancer (PC). The evaluation results are presented in Table 3 and show an elevated performance for the final system on the present database.

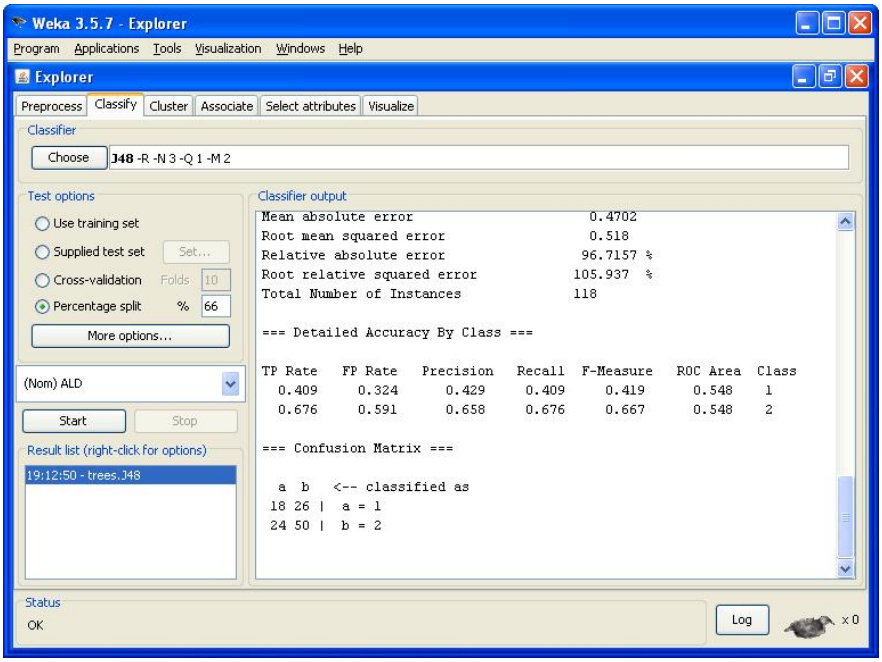



***Image 5.2*** *J48 Algorithm*

**Table 3.** Evaluation results for initial diagnosis of prostate cancer patients using HIROFILOS-I & II

| Metrics | SPECIALIZED DOCTOR | HIROFILOS-I | HIROFILOS-II |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **ACCURACY** | 0.95 | 0.76 | 0.93 |
| **SENSITIVITY** | 0.98 | 0.79 | 0.97 |
| **SPECIFICITY** | 0.99 | 0.75 | 0.99 |

### 5.8. Conclusions

In this paper, we present the design, implementation and evaluation of HIROFILOS-II, an intelligent system that deals with diagnosis and treatment of almost all prostate diseases. This is in contrast to existing efforts that mainly deal with prostate cancer only [3], [4], [5], [9]. The system comprises three modules, one dealing with LUTS, the other dealing with prostate diseases diagnosis process and the third concerning treatment proposals.

The predecessor of HIROFILOS-II, called HIROFILOS-I, was constructed based on expert knowledge only and using crisp rules. HIROFILOS-II has been constructed by extracting rules from a set of patient records via a machine learning algorithm (WEKA-J48) and transforming them into fuzzy rules taking account their medical usefulness. Additionally results from the machine learning algorithm showed that not all of the parameters identified by the expert are necessary for making decisions. Also, HIROFILOS-II has had a much better performance than HIROFILOS-I. On the other hand, the machine learning component will be periodically used to update existing rules based on new patient data gathered in the database.

At present, HIROFILOS-II is accommodated on a hospital server for use as: a decision-support system for resident doctors, as well as an e-learning platform for medical students. Furthermore, it can be used as an introductory advisory agent for interested patients having access through secure wireless network. In addition, more experiments are on the way as future steps in order to improve the system and to cover rare patient cases. Also, the extend of this system can be used as a model with other electronic health records in other hospitals of the country as well as other diseases.

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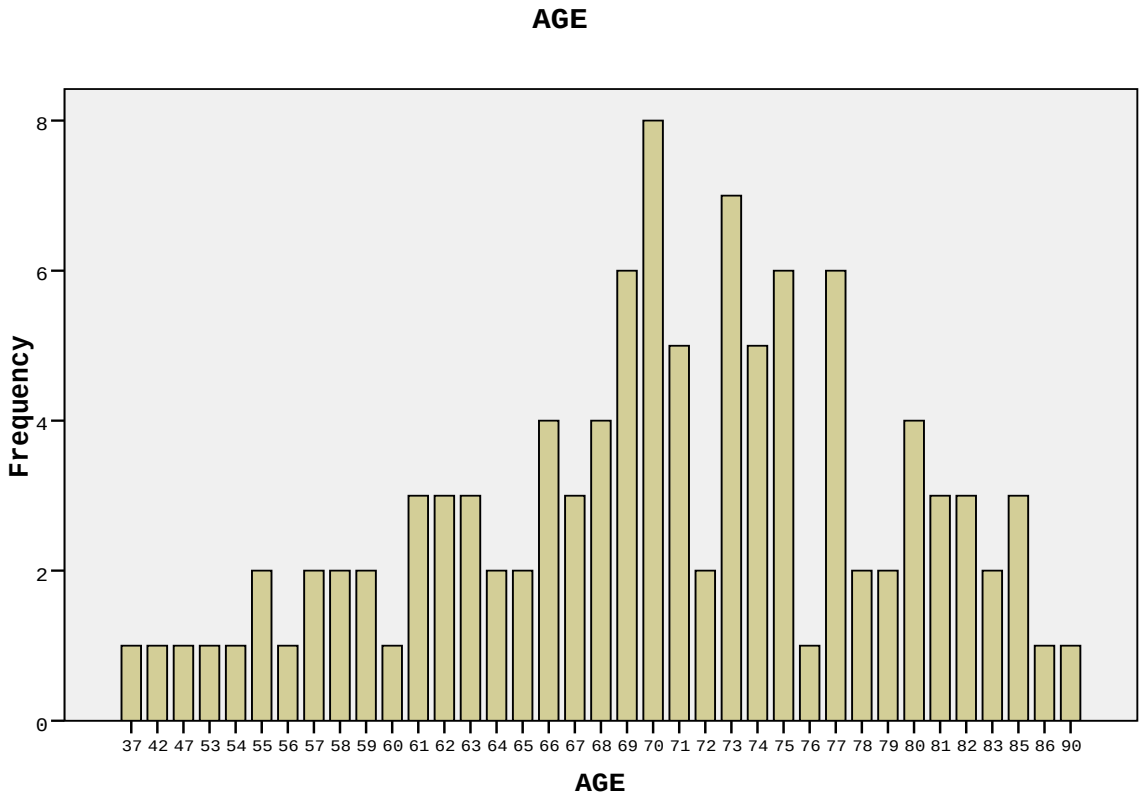
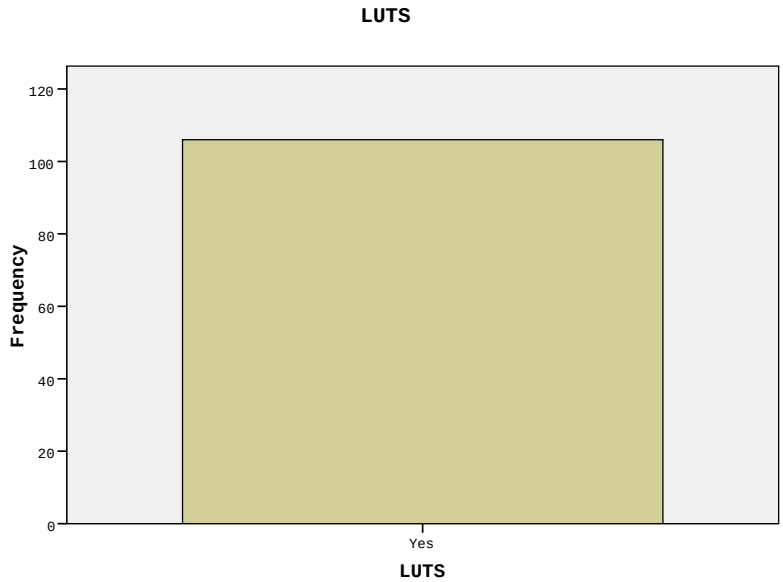
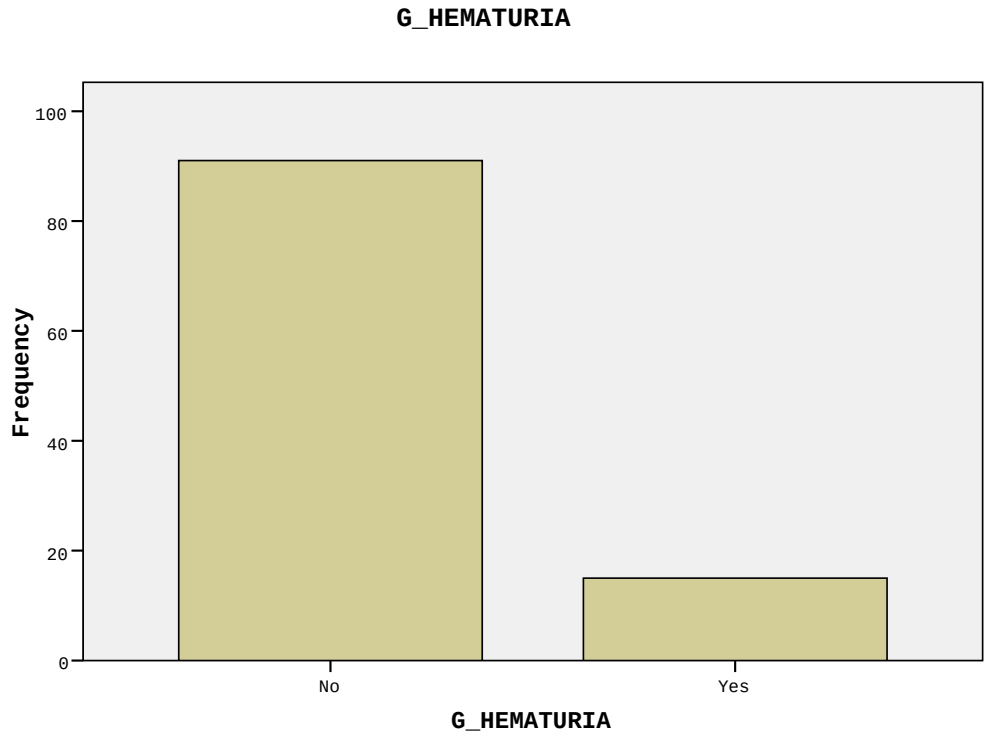
# APPENDIXES

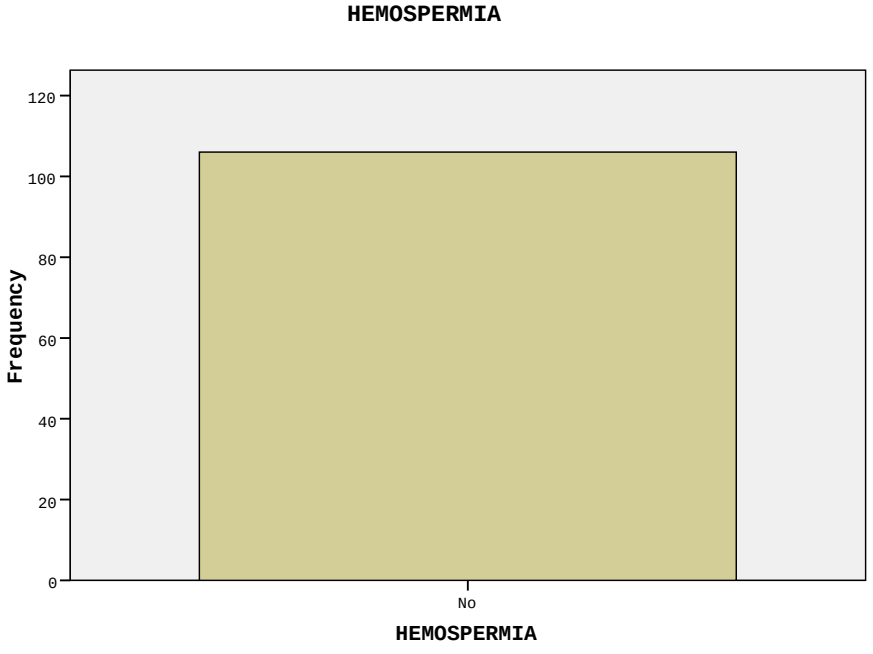
## APPENDIX I

*STATISTICS CONCERNING REAL PATIENT DATABASE USED FOR HIROFILOS I, II TRAINING AND TESTING*




G_HEMATURIA
100
80
60
40
20
0
Frequency
No
Yes
G_HEMATURIA


HEMOSPERMIA
120
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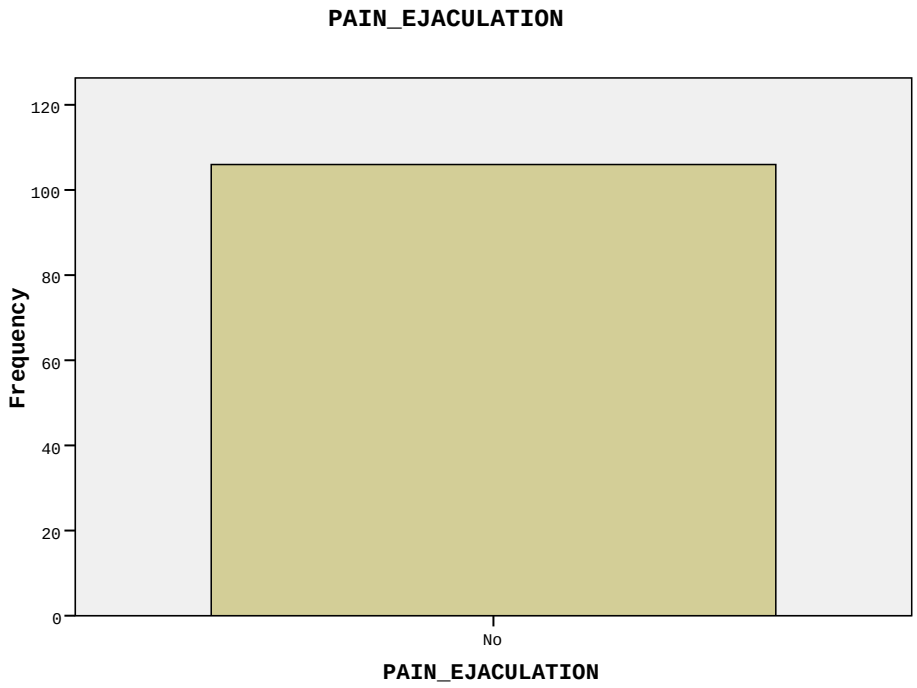
80
60
40
20
0
Frequency
No
HEMOSPERMIA


PAIN_EJACULATION
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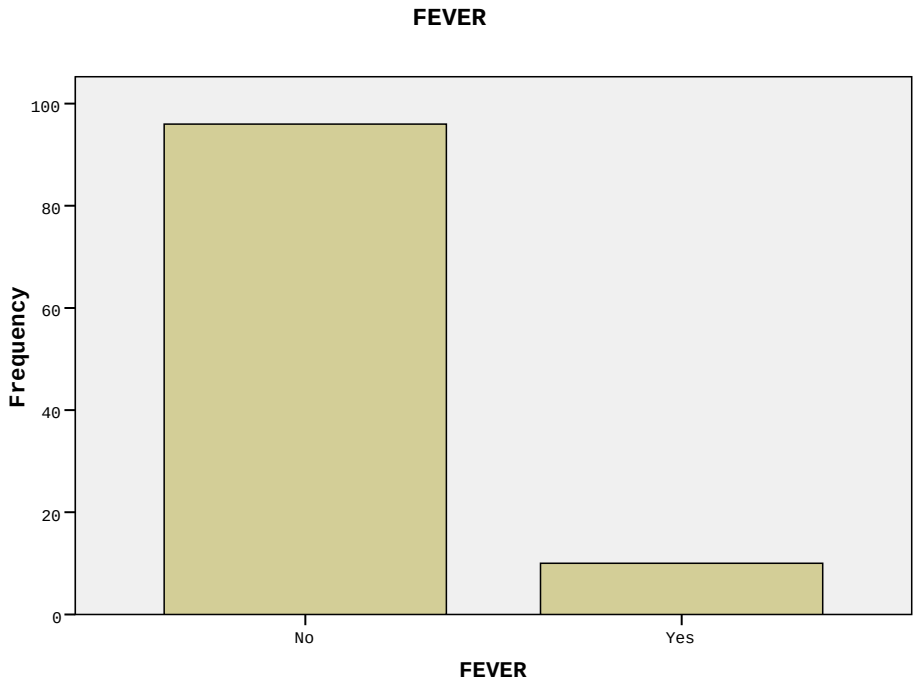
100
80
60
40
20
0
Frequency
No
PAIN_EJACULATION


FEVER
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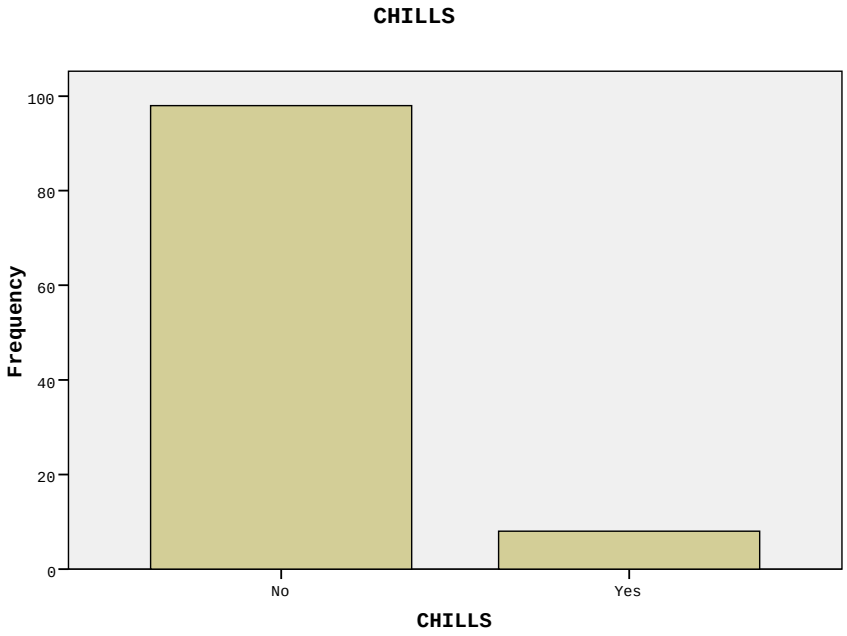
80
60
40
20
0
Frequency
No
Yes
FEVER


CHILLS
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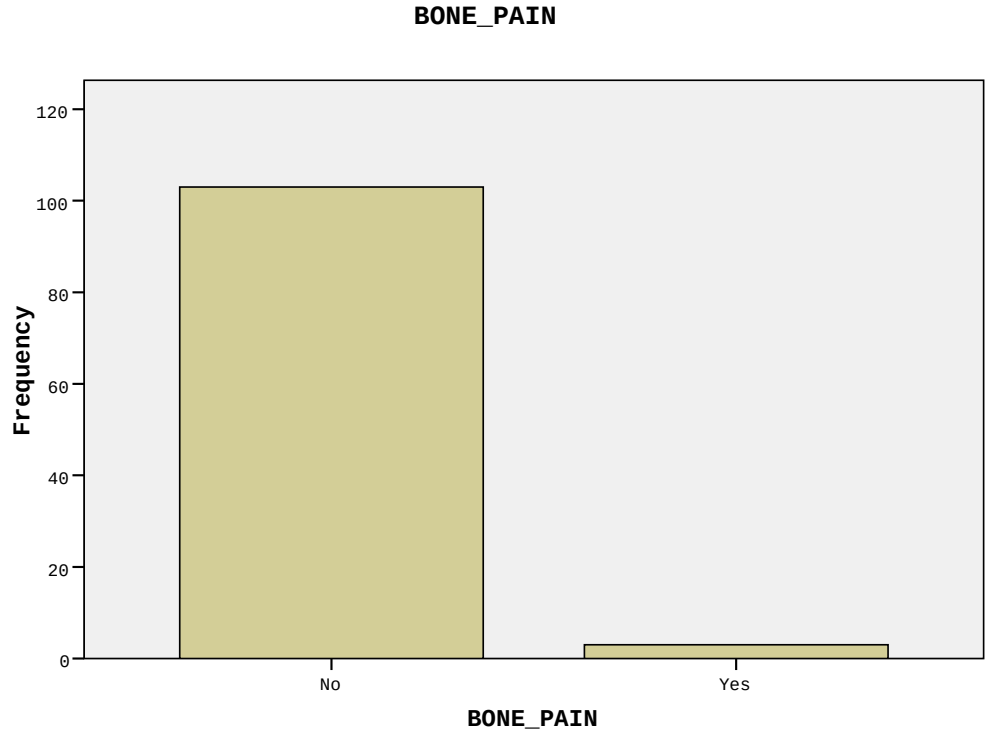
60
40
20
0
Frequency
No
Yes
CHILLS


BONE_PAIN
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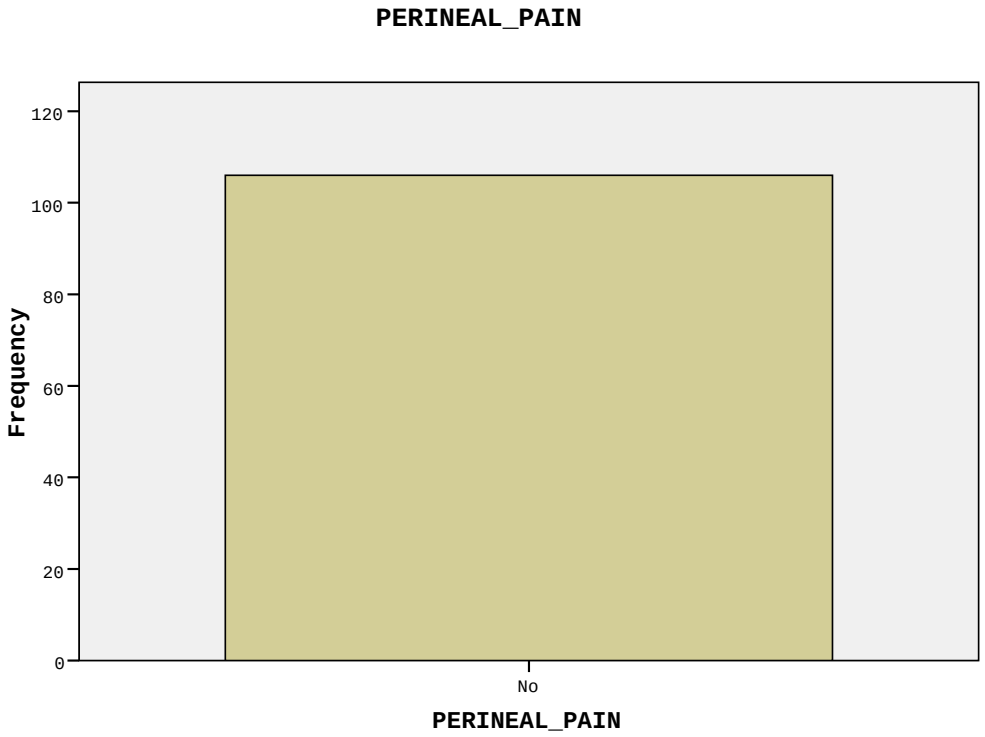
100
80
60
40
20
0
Frequency
No
Yes
BONE_PAIN


PERINEAL_PAIN
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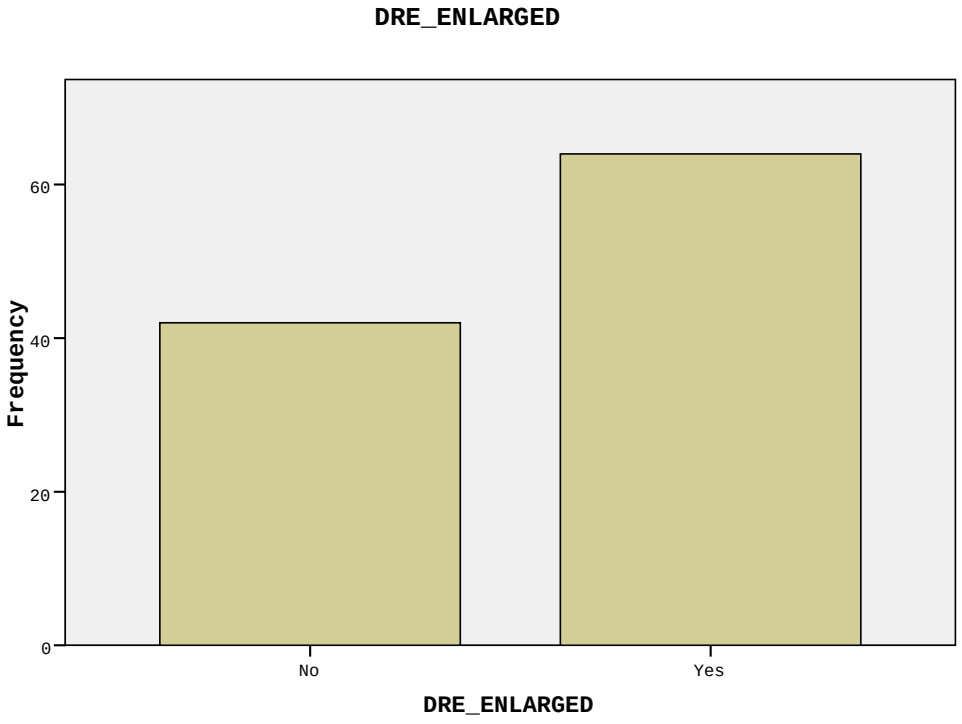
100
80
60
40
20
0
Frequency
No
PERINEAL_PAIN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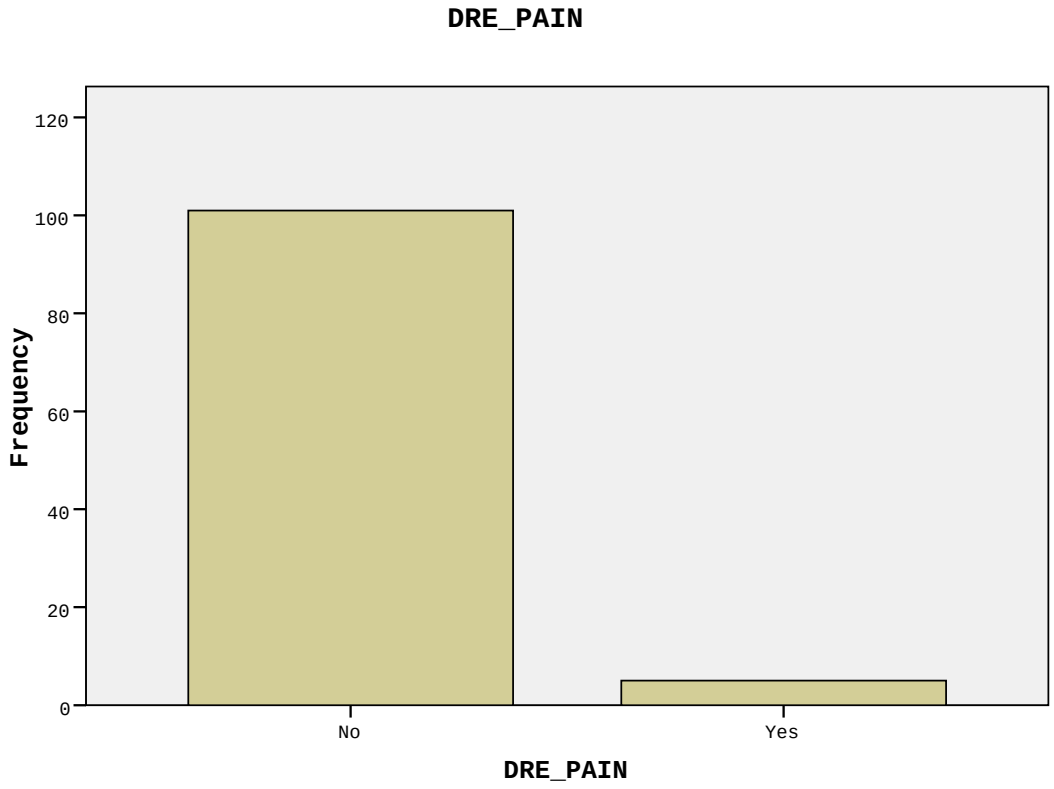
40
20
0
Frequency
No
Yes
DRE_ENLARGED


DRE_PAIN
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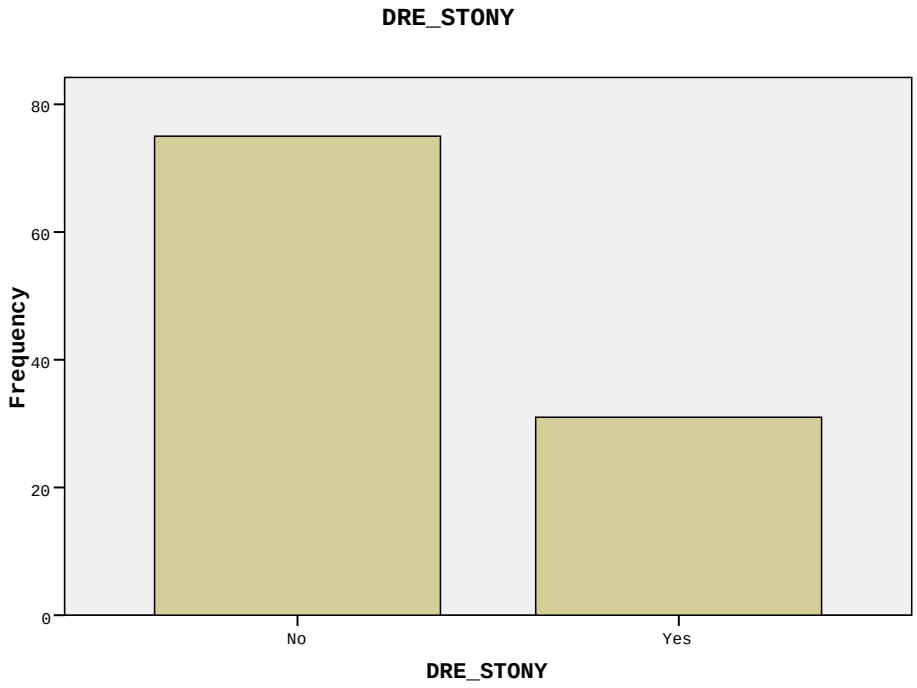
100
80
60
40
20
0
Frequency
No
Yes
DRE_PAIN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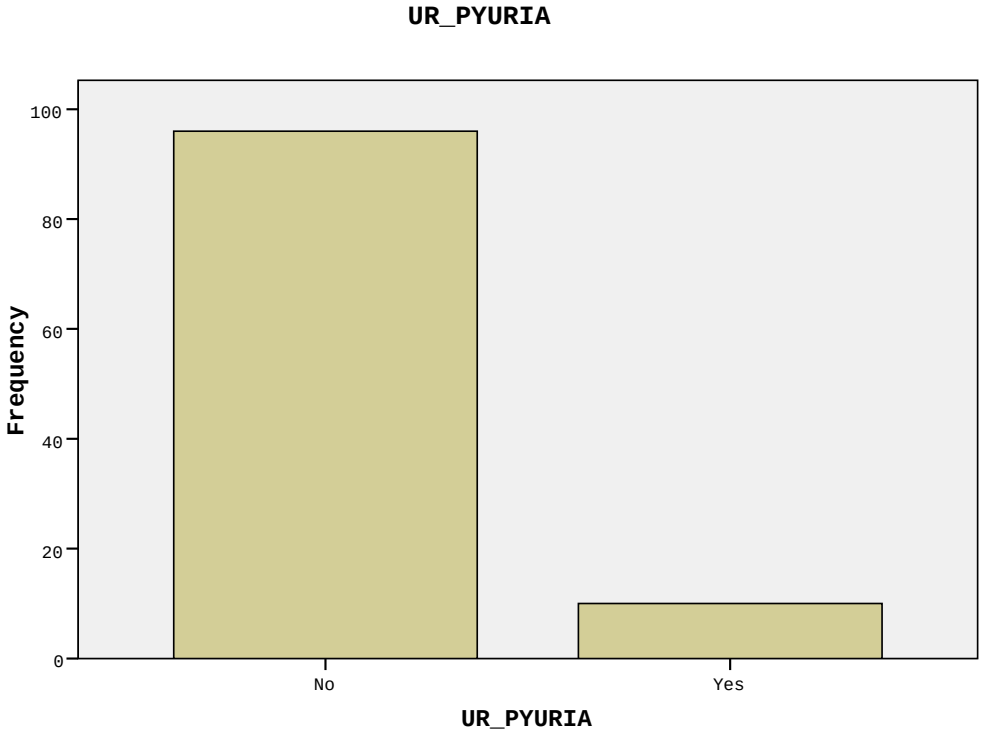
60
40
20
0
Frequency
No
Yes
DRE_STONY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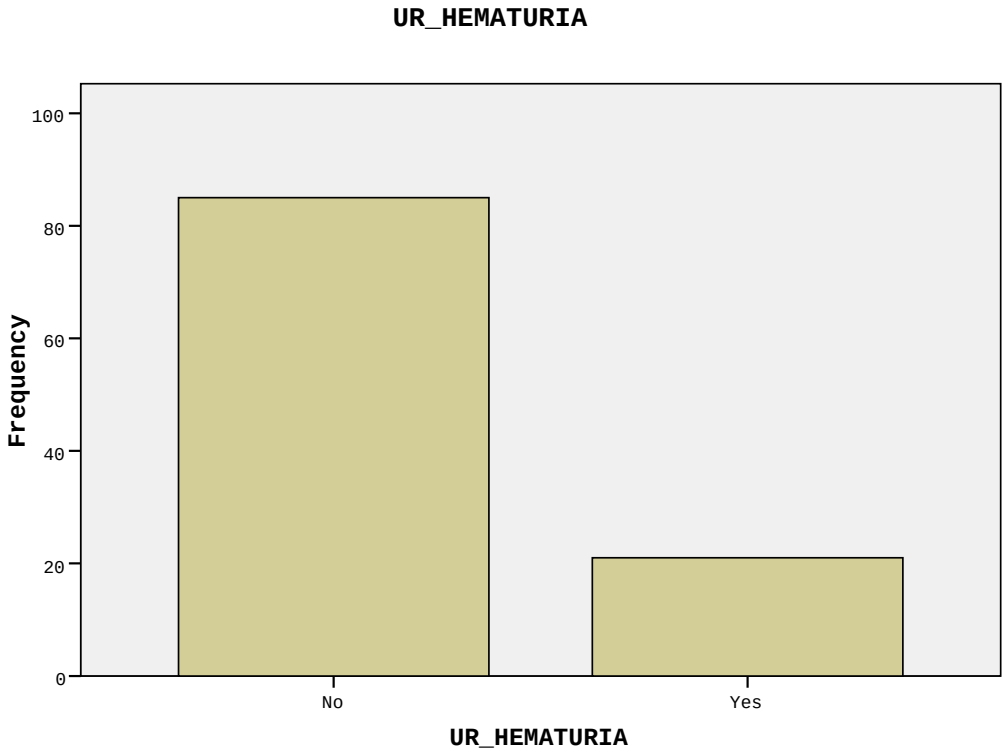
20
0
Frequency
No
Yes
UR_PYURIA


UR_HEMATURIA
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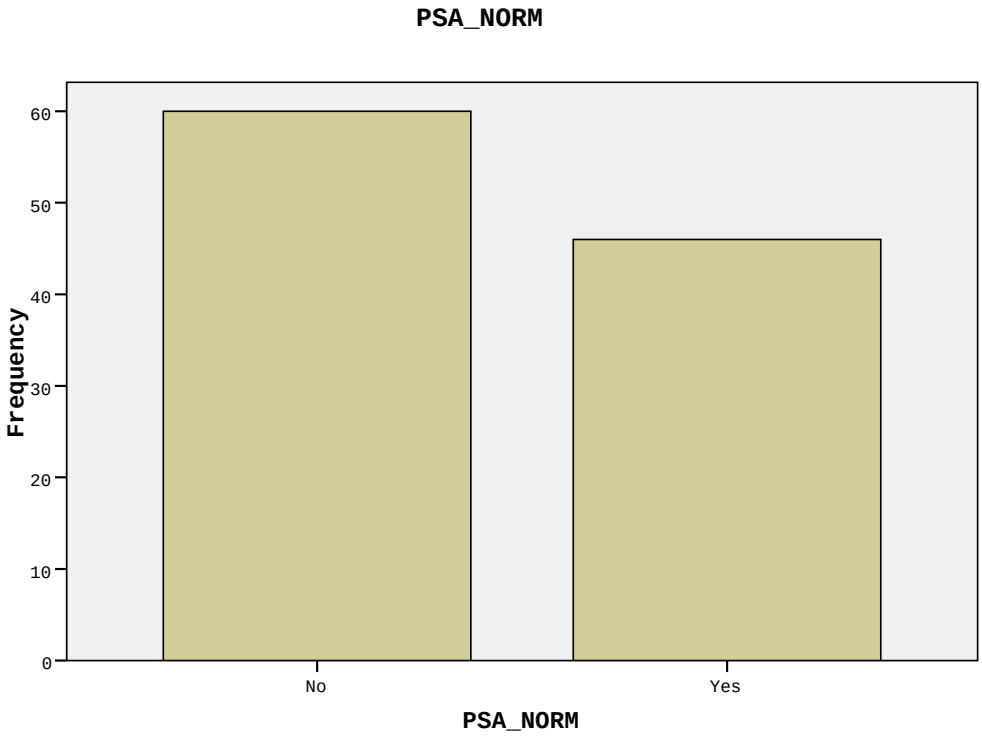
60
40
20
0
Frequency
No
Yes
UR_HEMATURIA


PSA_NORM
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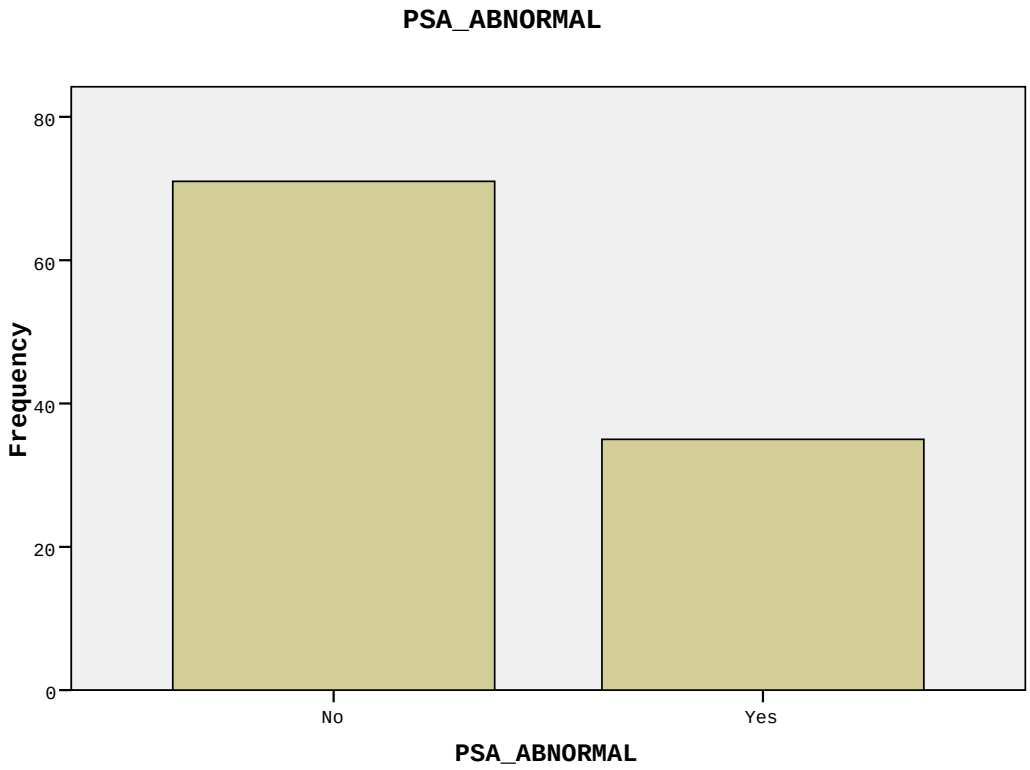
30
20
10
0
Frequency
No
Yes
PSA_NORM


PSA_ABNORMAL
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60
40
20
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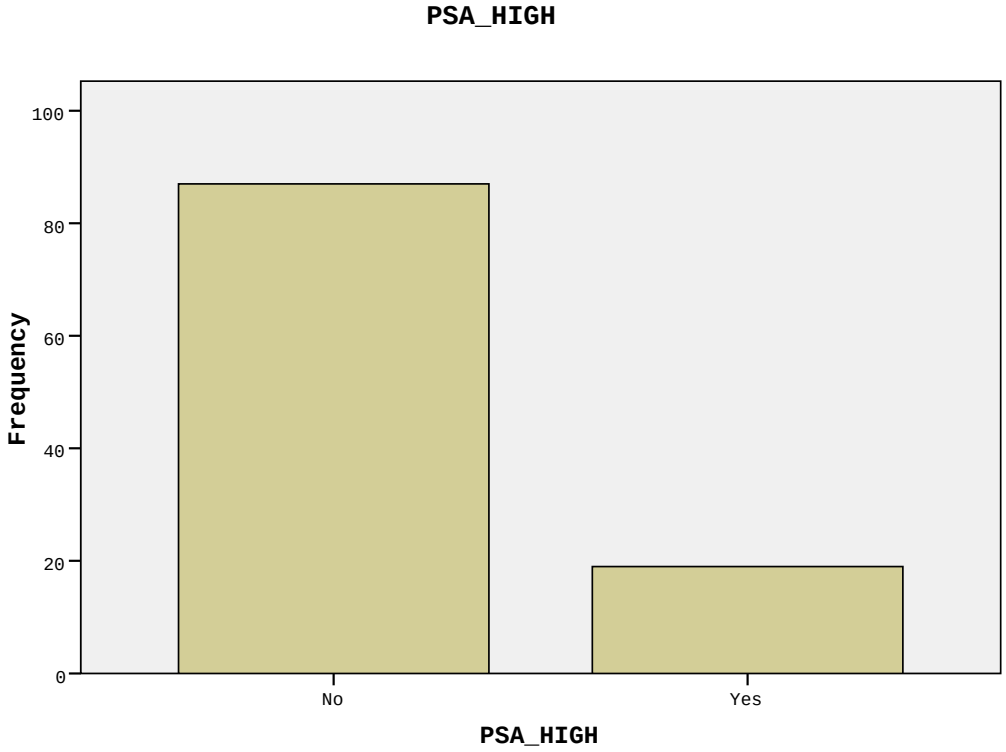
Frequency
No
Yes
PSA_ABNORMAL


PSA_HIGH
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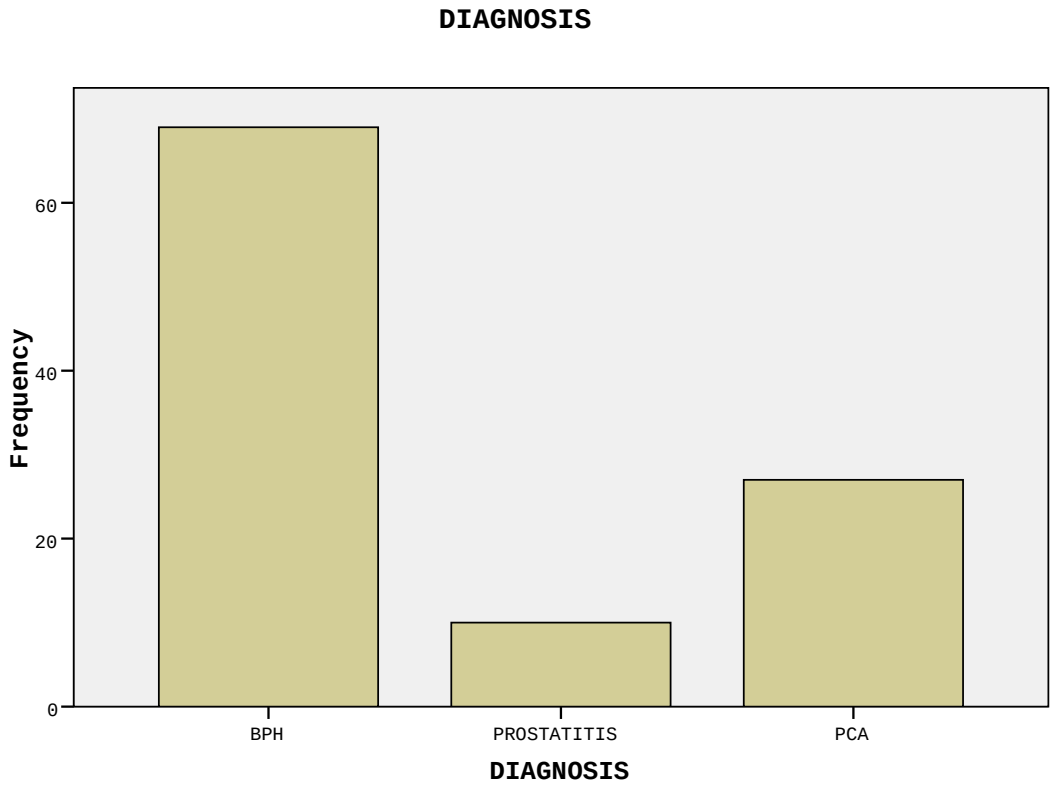
80
60
40
20
0
Frequency
No
Yes
PSA_HIGH


DIAGNOSIS
60
40
20
0
Frequency
BPH
PROSTATITIS
PCA
DIAGNOSIS

**APPENDIX II**

EXPERT SYSTEM RULES BEFORE IMPLEMENTETION IN CLIPS

1. If LUTS, then AP CP BHP PCA ()
2. If LUTS haematuria, then BHP PCA ()
3. If LUTS haemospermia, then CP PCA ()
4. If LUTS haematuria haemospermia, then PCA ()
5. If LUTS επωδυνη εκσεπρμ., then PCA ()
6. If LUTS haematuria επωδυνη εκσπερμ , then PCA ()
7. If LUTS haemospermia επωδυνη εκσπερμ, then PCA ()
8. If LUTS haematuria haemospermia επωδυνη εκσπερμ. then PCA ()
9. If LUTS fever, then PCA ()
10. If LUTS haematuria fever, then PCA ()
11. If LUTS haemospermia fever, then PCA ()
12. If LUTS haematuria haemospermia fever, then PCA ()
13. If LUTS επωδυνη εκσπερμ fever, then PCA ()
14. If LUTS haematuria επωδυνη εκσπερμ fever, then PCA ()
15. If LUTS haemospermia επωδυνη εκσπερμ fever, then PCA ()
16. If LUTS haematuria haemospermia επωδυνη εκσπερμ fever, then PCA ()
17. If LUTS fever με ριγος, then AP ()
18. If LUTS haematuria fever με ριγος, then AP ()
19. If LUTS πόνος στα οστά, then PCA ()
20. If LUTS haematuria πόνος στα οστά, then PCA ()
21. If LUTS haemospermia πόνος στα οστά, then PCA ()
22. If LUTS haematuria haemospermia πόνος στα οστά, then PCA ()
23. If LUTS επωδυνη εκσπερμ πόνος στα οστά, then PCA ()
24. If LUTS haematuria επώδυνη εκσπερμ πόνος στα οστά, then PCA ()
25. If LUTS haemospermia επωδυνη εκσπερμ πόνος στα οστά, then PCA ()
26. If LUTS haematuria haemospermia επωδυνη εκσπερμ πόνος στα οστά, then PCA ()
27. If LUTS fever πόνος στα οστά, then PCA ()
28. If LUTS haematuria fever πόνος στα οστά, then PCA ()
29. If LUTS haemospermia fever πόνος στα οστά, then PCA ()
30. If LUTS haematuria haemospermia fever πόνος στα οστά, then PCA ()
31. If LUTS επωδυνη εκσπερμ fever πόνος στα οστά, then PCA ()
32. If LUTS haematuria επωδυνη εκσπερμ fever πόνος στα οστά, then PCA ()
33. If LUTS haemospermia επωδυνη εκσπερμ fever πόνος στα οστά, then PCA ()
34. If LUTS haematuria haemospermia επωδυνη εκσπερμ fever πόνος στα οστά, then PCA ()
35. If LUTS πόνος στο περίνεο, then AP PCA ()
36. If LUTS haematuria πόνος στο περίνεο, then AP PCA ()
37. If LUTS haemospermia πόνος στο περίνεο, then PCA ()
38. If LUTS haematuria haemospermia πόνος στο περίνεο, then PCA ()
39. If LUTS επωδυνη εκσπερμ πόνος στο περίνεο, then PCA ()
40. If LUTS haematuria επωδυνη εκσπερμ πόνος στο περίνεο, then PCA ()
41. If LUTS haemospermia επωδυνη εκσπερμ πόνος στο περίνεο, then PCA ()
42. If LUTS haematuria haemospermia επωδυνη εκσπερμ πόνος στο περίνεο, then PCA ()
43. If LUTS fever πόνος στο περίνεο, then PCA ()

44. If LUTS haematuria fever πόνος στο περίνεο, then PCA ()
45. If LUTS haemospermia fever πόνος στο περίνεο, then PCA ()
46. If LUTS haematuria haemospermia fever πόνος στο περίνεο, then PCA ()
47. If LUTS επωδυνη εκσπερμ fever πόνος στο περίνεο, then PCA ()
48. If LUTS haematuria επωδυνη εκσπερμ fever πόνος στο περίνεο, then PCA ()
49. If LUTS haemospermia επωδυνη εκσπερμ fever πόνος στο περίνεο, then PCA ()
50. If LUTS haematuria haemospermia επωδυνη εκσπερμ fever πόνος στο περίνεο, then PCA ()
51. If LUTS fever με ρίγος πόνος στο περίνεο, then AP ()
52. If LUTS fever με ρίγος haematuria πόνος στο περίνεο, then AP ()
53. If LUTS πόνος στα οστά πόνος στο περίνεο, then PCA ()
54. If LUTS haematuria πόνος στα οστά πόνος στο περίνεο, then PCA ()
55. If LUTS haemospermia πόνος στα οστά πόνος στο περίνεο, then PCA ()
56. If LUTS haematuria haemospermia πόνος στα οστά πόνος στο περίνεο, then PCA ()
57. If LUTS επωδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο, then PCA ()
58. If LUTS haematuria επωδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο, then PCA ()
59. If LUTS haemospermia επωδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο, then PCA ()
60. If LUTS haematuria haemospermia επωδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο, then PCA ()
61. If LUTS fever πόνος στα οστά πόνος στο περίνεο, then PCA ()
62. If LUTS haematuria fever πόνος στα οστά πόνος στο περίνεο, then PCA ()
63. If LUTS haemospermia fever πόνος στα οστά πόνος στο περίνεο, then PCA ()
64. If LUTS haematuria haemospermia fever πόνος στα οστά πόνος στο περίνεο, then PCA ()
65. If LUTS επωδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο, then PCA ()
66. If LUTS haematuria επωδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο, then PCA ()
67. If LUTS haemospermia επωδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο, then PCA ()
68. If LUTS haematuria haemospermia επωδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο, then PCA ()
69. If LUTS μεγάλο μαλακό DRE, then BHP ()
70. If LUTS haematuria μεγάλο μαλακό DRE, then BHP ()
71. If LUTS επώδυνος DRE, then AP CP ()
72. If LUTS haematuria επώδυνος DRE, then AP ()
73. If LUTS haemospermia επώδυνος DRE, then CP ()
74. If LUTS fever με ρίγος επώδυνος DRE, then AP ()
75. If LUTS haematuria fever με ρίγος επώδυνος DRE, then AP ()
76. If LUTS πόνος στο περίνεο επώδυνος DRE, then AP ()
77. If LUTS haematuria πόνος στο περίνεο επώδυνος DRE, then AP ()
78. If LUTS fever με ρίγος πόνος στο περίνεο επώδυνος DRE, then AP ()
79. If LUTS haematuria fever με ρίγος πόνος στο περίνεο επώδυνος DRE, then AP ()
80. If LUTS σκληρός DRE, then PCA ()

81. If LUTS haematuria σκληρός DRE, then PCA ()
82. If LUTS haemospermia σκληρός DRE, then PCA ()
83. If LUTS haematuria haemospermia σκληρός DRE, then PCA ()
84. If LUTS επώδυνη εκσπερμ. σκληρός DRE, then PCA ()
85. If LUTS haematuria επώδυνη εκσπερμ. σκληρός DRE, then PCA ()
86. If LUTS haemospermia επώδυνη εκσπερμ. σκληρός DRE, then PCA ()
87. If LUTS haematuria haemospermia επώδυνη εκσπερμ. σκληρός DRE, then PCA ()
88. If LUTS fever σκληρός DRE, then PCA ()
89. If LUTS haematuria fever σκληρός DRE, then PCA ()
90. If LUTS haemospermia fever σκληρός DRE, then PCA ()
91. If LUTS haematuria haemospermia fever σκληρός DRE, then PCA ()
92. If LUTS επώδυνη εκσπερμ. fever σκληρός DRE, then PCA ()
93. If LUTS haematuria επώδυνη εκσπερμ. fever σκληρός DRE, then PCA ()
94. If LUTS haemospermia επώδυνη εκσπερμ. fever σκληρός DRE, then PCA ()
95. If LUTS haematuria haemospermia επώδυνη εκσπερμ. fever σκληρός DRE, then PCA ()
96. If LUTS πόνος στα οστά σκληρός DRE, then PCA ()
97. If LUTS haematuria πόνος στα οστά σκληρός DRE, then PCA ()
98. If LUTS haemospermia πόνος στα οστά σκληρός DRE, then PCA ()
99. If LUTS haematuria haemospermia πόνος στα οστά σκληρός DRE, then PCA ()
100. If LUTS επώδυνη εκσπερμ. πόνος στα οστά σκληρός DRE, then PCA ()
101. If LUTS haematuria επώδυνη εκσπερμ. πόνος στα οστά σκληρός DRE, then PCA ()
102. If LUTS haemospermia επώδυνη εκσπερμ. πόνος στα οστά σκληρός DRE, then PCA ()
103. If LUTS haematuria haemospermia επώδυνη εκσπερμ. πόνος στα οστά σκληρός DRE, then PCA ()
104. If LUTS fever πόνος στα οστά σκληρός DRE, then PCA ()
105. If LUTS haematuria fever πόνος στα οστά σκληρός DRE, then PCA ()
106. If LUTS haemospermia fever πόνος στα οστά σκληρός DRE, then PCA ()
107. If LUTS haematuria haemospermia fever πόνος στα οστά σκληρός DRE, then PCA ()
108. If LUTS επώδυνη εκσπερμ. fever πόνος στα οστά σκληρός DRE, then PCA ()
109. If LUTS haematuria επώδυνη εκσπερμ. fever πόνος στα οστά σκληρός DRE, then PCA ()
110. If LUTS haemospermia επώδυνη εκσπερμ. fever πόνος στα οστά σκληρός DRE, then PCA ()
111. If LUTS haematuria haemospermia επώδυνη εκσπερμ. fever πόνος στα οστά σκληρός DRE, then PCA ()
112. If LUTS πόνος στο περίνεο σκληρός DRE, then PCA ()
113. If LUTS haematuria πόνος στο περίνεο σκληρός DRE, then PCA ()
114. If LUTS haemospermia πόνος στο περίνεο σκληρός DRE, then PCA ()

115. If LUTS haematuria haemospermia πόνος στο περίνεο σκληρός DRE, then PCA ()
116. If LUTS επώδυνη εκσπερμ. πόνος στο περίνεο σκληρός DRE, then PCA ()
117. If LUTS haematuria επώδυνη εκσπερμ πόνος στο περίνεο σκληρός DRE, then PCA ()
118. If LUTS haemospermia επώδυνη εκσπερμ πόνος στο περίνεο σκληρός DRE, then PCA ()
119. If LUTS haematuria haemospermia επώδυνη εκσπερμ πόνος στο περίνεο σκληρός DRE, then PCA ()
120. If LUTS fever πόνος στο περίνεο σκληρός DRE, then PCA ()
121. If LUTS haematuria fever πόνος στο περίνεο σκληρός DRE, then PCA ()
122. If LUTS haemospermia fever πόνος στο περίνεο σκληρός DRE, then PCA ()
123. If LUTS haematuria haemospermia fever πόνος στο περίνεο σκληρός DRE, then PCA ()
124. If LUTS επώδυνη εκσπερμ fever πόνος στο περίνεο σκληρός DRE, then PCA ()
125. If LUTS haematuria επώδυνη εκσπερμ fever πόνος στο περίνεο σκληρός DRE, then PCA ()
126. If LUTS haemospermia επώδυνη εκσπερμ fever πόνος στο περίνεο σκληρός DRE, then PCA ()
127. If LUTS haematuria haemospermia επώδυνη εκσπερμ fever πόνος στο περίνεο σκληρός DRE, then PCA ()
128. If LUTS πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
129. If LUTS haematuria πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
130. If LUTS haemospermia πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
131. If LUTS haematuria haemospermia πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
132. If LUTS επώδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
133. If LUTS haematuria επώδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
134. If LUTS haemospermia επώδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
135. If LUTS haematuria haemospermia επώδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
136. If LUTS fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
137. If LUTS haematuria fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
138. If LUTS haemospermia fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
139. If LUTS haematuria haemospermia fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()

140. If LUTS επώδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
141. If LUTS haematuria επώδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
142. If LUTS haemospermia επώδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
143. If LUTS haematuria haemospermia επώδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE, then PCA ()
144. If LUTS πυουρία, then AP CP ()
145. If LUTS haematuria πυουρία, then AP ()
146. If LUTS haemospermia πυουρία, then CP ()
147. If LUTS fever με ρίγος πυουρία, then AP ()
148. If LUTS haematuria fever με ρίγος πυουρία, then AP ()
149. If LUTS πόνος στο περίνεο πυουρία, then AP ()
150. If LUTS haematuria πόνος στο περίνεο πυουρία, then AP ()
151. If LUTS fever με ρίγος πόνος στο περίνεο πυουρία, then AP ()
152. If LUTS haematuria fever με ρίγος πόνος στο περίνεο πυουρία, then AP ()
153. If LUTS επώδυνος DRE πυουρία, then AP CP ()
154. If LUTS haematuria επώδυνος DRE πυουρία, then AP ()
155. If LUTS haemospermia επώδυνος DRE πυουρία, then CP ()
156. If LUTS fever με ρίγος επώδυνος DRE πυουρία, then AP ()
157. If LUTS haematuria fever με ρίγος επώδυνος DRE πυουρία, then AP ()
158. If LUTS πόνος στο περίνεο επώδυνος DRE πυουρία, then AP ()
159. If LUTS haematuria πόνος στο περίνεο επώδυνος DRE πυουρία, then AP ()
160. If LUTS fever με ρίγος πόνος στο περίνεο επώδυνος DRE πυουρία, then AP ()
161. If LUTS haematuria fever με ρίγος πόνος στο περίνεο επώδυνος DRE πυουρία, then AP ()
162. If LUTS PSA<4ngr/ml, then CP BHP ()
163. If LUTS haematuria PSA<4ngr/ml, then BHP ()
164. If LUTS haemospermia PSA<4ngr/ml, then CP ()
165. If LUTS μεγάλο μαλακό DRE PSA<4ngr/ml, then BHP ()
166. If LUTS haematuria μεγάλο μαλακό DRE PSA<4ngr/ml, then BHP ()
167. If LUTS επώδυνος DRE PSA<4ngr/ml, then CP ()
168. If LUTS haemospermia επώδυνος DRE PSA<4ngr/ml, then CP ()
169. If LUTS πυουρία PSA<4ngr/ml, then CP ()
170. If LUTS haemospermia πυουρία PSA<4ngr/ml, then CP ()
171. If LUTS επώδυνος DRE πυουρία PSA<4ngr/ml, then CP ()
172. If LUTS haemospermia επώδυνος DRE πυουρία PSA<4ngr/ml, then CP ()
173. If LUTS PSA>4ngr/ml, then AP BHP PCA ()**, else biopsy**
174. If LUTS haematuria PSA>4ngr/ml, then BHP PCA (), **else biopsy**
175. If LUTS haemospermia PSA>4ngr/ml, then PCA ()
176. If LUTS haematuria haemospermia PSA>4ngr/ml, then PCA ()
177. If LUTS επωδυνη εκσπερμ. PSA>4ngr/ml, then PCA ()
178. If LUTS haematuria επωδυνη εκσπερμ PSA>4ngr/ml, then PCA ()
179. If LUTS haemospermia επωδυνη εκσπερμ PSA>4ngr/ml, then PCA ()

180. If LUTS haematuria haemospermia επωδυνη εκσπερμ PSA>4ngr/ml,,. then PCA ()
181. If LUTS fever PSA>4ngr/ml, then PCA ()
182. If LUTS haematuria fever PSA>4ngr/ml, then PCA ()
183. If LUTS haemospermia fever PSA>4ngr/ml, then PCA ()
184. If LUTS haematuria haemospermia fever PSA>4ngr/ml, then PCA ()
185. If LUTS επωδυνη εκσπερμ fever PSA>4ngr/ml, then PCA ()
186. If LUTS haematuria επωδυνη εκσπερμ fever PSA>4ngr/ml, then PCA ()
187. If LUTS haemospermia επωδυνη εκσπερμ fever PSA>4ngr/ml, then PCA ()
188. If LUTS haematuria haemospermia επωδυνη εκσπερμ fever PSA>4ngr/ml, then PCA ()
189. If LUTS πόνος στα οστά PSA>4ngr/ml , then PCA ()
190. If LUTS haematuria πόνος στα οστά PSA>4ngr/ml , then PCA ()
191. If LUTS haemospermia πόνος στα οστά PSA>4ngr/ml , then PCA ()
192. If LUTS haematuria haemospermia πόνος στα οστά PSA>4ngr/ml , then PCA ()
193. If LUTS επωδυνη εκσπερμ πόνος στα οστά PSA>4ngr/ml, then PCA ()
194. If LUTS haematuria επωδυνη εκσπερμ πόνος στα οστά PSA>4ngr/ml, then PCA ()
195. If LUTS haemospermia επωδυνη εκσπερμ πόνος στα οστά PSA>4ngr/ml, then PCA ()
196. If LUTS haematuria haemospermia επωδυνη εκσπερμ πόνος στα οστά PSA>4ngr/ml, then PCA ()
197. If LUTS fever πόνος στα οστά PSA>4ngr/ml, then PCA ()
198. If LUTS haematuria fever πόνος στα οστά PSA>4ngr/ml, then PCA ()
199. If LUTS haemospermia fever πόνος στα οστά PSA>4ngr/ml, then PCA ()
200. If LUTS haematuria haemospermia fever πόνος στα οστά PSA>4ngr/ml, then PCA ()
201. If LUTS επωδυνη εκσπερμ fever πόνος στα οστά PSA>4ngr/ml, then PCA ()
202. If LUTS haematuria επωδυνη εκσπερμ fever πόνος στα οστά PSA>4ngr/ml, then PCA ()
203. If LUTS haemospermia επωδυνη εκσπερμ fever πόνος στα οστά PSA>4ngr/ml, then PCA ()
204. If LUTS haematuria haemospermia επωδυνη εκσπερμ fever πόνος στα οστά PSA>4ngr/ml, then PCA ()
205. If LUTS πόνος στο περίνεο PSA>4ngr/ml, then AP PCA (), else biopsy
206. If LUTS haematuria πόνος στο περίνεο PSA>4ngr/ml, then AP PCA (), else biopsy
207. If LUTS haemospermia πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
208. If LUTS haematuria haemospermia πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
209. If LUTS επωδυνη εκσπερμ πόνος στο περίνεο PSA>4ngr/ml, then PCA ()

210. If LUTS haematuria επωδυνη εκσπερμ πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
211. If LUTS haemospermia επωδυνη εκσπερμ πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
212. If LUTS haematuria haemospermia επωδυνη εκσπερμ πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
213. If LUTS fever πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
214. If LUTS haematuria fever πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
215. If LUTS haemospermia fever πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
216. If LUTS haematuria haemospermia fever πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
217. If LUTS επωδυνη εκσπερμ fever πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
218. If LUTS haematuria επωδυνη εκσπερμ fever πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
219. If LUTS haemospermia επωδυνη εκσπερμ fever πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
220. If LUTS haematuria haemospermia επωδυνη εκσπερμ fever πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
221. If LUTS πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
222. If LUTS haematuria πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
223. If LUTS haemospermia πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
224. If LUTS haematuria haemospermia πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
225. If LUTS επωδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
226. If LUTS haematuria επωδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
227. If LUTS haemospermia επωδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
228. If LUTS haematuria haemospermia επωδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
229. If LUTS fever πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
230. If LUTS haematuria fever πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
231. If LUTS haemospermia fever πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
232. If LUTS haematuria haemospermia fever πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
233. If LUTS επωδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
234. If LUTS haematuria επωδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()

235. If LUTS haemospermia επωδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
236. If LUTS haematuria haemospermia επωδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο PSA>4ngr/ml, then PCA ()
237. If LUTS επώδυνος DRE PSA>4ngr/ml, then CP ()
238. If LUTS haematuria επώδυνος DRE PSA>4ngr/ml, then AP ()
239. If LUTS fever με ρίγος επώδυνος DRE PSA>4ngr/ml, then AP ()
240. If LUTS haematuria fever με ρίγος επώδυνος DRE PSA>4ngr/ml, then AP ()
241. If LUTS πόνος στο περίνεο επώδυνος DRE PSA>4ngr/ml, then AP ()
242. If LUTS haematuria πόνος στο περίνεο επώδυνος DRE PSA>4ngr/ml, then AP ()
243. If LUTS fever με ρίγος πόνος στο περίνεο επώδυνος DRE PSA>4ngr/ml, then AP ()
244. If LUTS haematuria fever με ρίγος πόνος στο περίνεο επώδυνος DRE PSA>4ngr/ml, then AP ()
245. If LUTS σκληρός DRE PSA>4ngr/ml, then PCA ()
246. If LUTS haematuria σκληρός DRE PSA>4ngr/ml, then PCA ()
247. If LUTS haemospermia σκληρός DRE PSA>4ngr/ml, then PCA ()
248. If LUTS haematuria haemospermia σκληρός DRE PSA>4ngr/ml, then PCA ()
249. If LUTS επώδυνη εκσπερμ. σκληρός DRE PSA>4ngr/ml, then PCA ()
250. If LUTS haematuria επώδυνη εκσπερμ. σκληρός DRE PSA>4ngr/ml, then PCA ()
251. If LUTS haemospermia επώδυνη εκσπερμ. σκληρός DRE PSA>4ngr/ml, then PCA ()
252. If LUTS haematuria haemospermia επώδυνη εκσπερμ. σκληρός DRE PSA>4ngr/ml, then PCA ()
253. If LUTS fever σκληρός DRE PSA>4ngr/ml, then PCA ()
254. If LUTS haematuria fever σκληρός DRE PSA>4ngr/ml, then PCA ()
255. If LUTS haemospermia fever σκληρός DRE PSA>4ngr/ml, then PCA ()
256. If LUTS haematuria haemospermia fever σκληρός DRE PSA>4ngr/ml, then PCA ()
257. If LUTS επώδυνη εκσπερμ. fever σκληρός DRE PSA>4ngr/ml, then PCA ()
258. If LUTS haematuria επώδυνη εκσπερμ. fever σκληρός DRE PSA>4ngr/ml, then PCA ()
259. If LUTS haemospermia επώδυνη εκσπερμ. fever σκληρός DRE PSA>4ngr/ml, then PCA ()
260. If LUTS haematuria haemospermia επώδυνη εκσπερμ. fever σκληρός DRE PSA>4ngr/ml, then PCA ()
261. If LUTS πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
262. If LUTS haematuria πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
263. If LUTS haemospermia πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
264. If LUTS haematuria haemospermia πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()

265. If LUTS επώδυνη εκσπερμ. πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
266. If LUTS haematuria επώδυνη εκσπερμ. πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
267. If LUTS haemospermia επώδυνη εκσπερμ. πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
268. If LUTS haematuria haemospermia επώδυνη εκσπερμ. πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
269. If LUTS fever πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
270. If LUTS haematuria fever πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
271. If LUTS haemospermia fever πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
272. If LUTS haematuria haemospermia fever πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
273. If LUTS επώδυνη εκσπερμ. fever πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
274. If LUTS haematuria επώδυνη εκσπερμ. fever πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
275. If LUTS haemospermia επώδυνη εκσπερμ. fever πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
276. If LUTS haematuria haemospermia επώδυνη εκσπερμ. fever πόνος στα οστά σκληρός DRE PSA>4ngr/ml, then PCA ()
277. If LUTS πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
278. If LUTS haematuria πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
279. If LUTS haemospermia πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
280. If LUTS haematuria haemospermia πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
281. If LUTS επώδυνη εκσπερμ. πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
282. If LUTS haematuria επώδυνη εκσπερμ πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
283. If LUTS haemospermia επώδυνη εκσπερμ πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
284. If LUTS haematuria haemospermia επώδυνη εκσπερμ πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
285. If LUTS fever πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
286. If LUTS haematuria fever πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
287. If LUTS haemospermia fever πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
288. If LUTS haematuria haemospermia fever πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
289. If LUTS επώδυνη εκσπερμ fever πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()

290. If LUTS haematuria επώδυνη εκσπερμ fever πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
291. If LUTS haemospermia επώδυνη εκσπερμ fever πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
292. If LUTS haematuria haemospermia επώδυνη εκσπερμ fever πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
293. If LUTS πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
294. If LUTS haematuria πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
295. If LUTS haemospermia πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
296. If LUTS haematuria haemospermia πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
297. If LUTS επώδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
298. If LUTS haematuria επώδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
299. If LUTS haemospermia επώδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
300. If LUTS haematuria haemospermia επώδυνη εκσπερμ πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
301. If LUTS fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
302. If LUTS haematuria fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
303. If LUTS haemospermia fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
304. If LUTS haematuria haemospermia fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
305. If LUTS επώδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
306. If LUTS haematuria επώδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
307. If LUTS haemospermia επώδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
308. If LUTS haematuria haemospermia επώδυνη εκσπερμ fever πόνος στα οστά πόνος στο περίνεο σκληρός DRE PSA>4ngr/ml, then PCA ()
309. If LUTS πυουρία PSA>4ngr/ml, then AP ()
310. If LUTS haematuria πυουρία PSA>4ngr/ml, then AP ()
311. If LUTS fever με ρίγος πυουρία PSA>4ngr/ml, then AP ()
312. If LUTS haematuria fever με ρίγος πυουρία PSA>4ngr/ml, then AP ()
313. If LUTS πόνος στο περίνεο πυουρία PSA>4ngr/ml, then AP ()
314. If LUTS haematuria πόνος στο περίνεο πυουρία PSA>4ngr/ml, then AP ()
315. If LUTS fever με ρίγος πόνος στο περίνεο πυουρία PSA>4ngr/ml, then AP ()
316. If LUTS haematuria fever με ρίγος πόνος στο περίνεο πυουρία PSA>4ngr/ml, then AP ()

317. If LUTS επώδυνος DRE πυουρία PSA>4ngr/ml, then AP ()
318. If LUTS haematuria επώδυνος DRE πυουρία PSA>4ngr/ml, then AP ()
319. If LUTS fever με ρίγος επώδυνος DRE πυουρία PSA>4ngr/ml, then AP ()
320. If LUTS haematuria fever με ρίγος επώδυνος DRE πυουρία PSA>4ngr/ml, then AP ()
321. If LUTS πόνος στο περίνεο επώδυνος DRE πυουρία PSA>4ngr/ml, then AP ()
322. If LUTS haematuria πόνος στο περίνεο επώδυνος DRE πυουρία PSA>4ngr/ml, then AP ()
323. If LUTS fever με ρίγος πόνος στο περίνεο επώδυνος DRE πυουρία PSA>4ngr/ml, then AP ()
324. If LUTS haematuria fever με ρίγος πόνος στο περίνεο επώδυνος DRE πυουρία PSA>4ngr/ml, then AP ()

**APPENDIX II**

*RULES FOR HIROFILOS I EXPERT SYSTEM IMPLEMENTED IN FUZZYCLIPS*

**1. LUTS DIAGNOSIS RULES**

```
;++++++++++++++++++++++++++++++++++++++++++++++++++++++
;++++++++++++L U T S++++++++++++++++++++++++++++++++
;++++++++++++++++++++++++++++++++++++++++++++++++++++++


deffunction ask-question (?question $?allowed-values)
   (printout t ?question)
   (bind ?answer (read))
   (if (lexemep ?answer)
    then (bind ?answer (lowcase ?answer)))
   (while (not (member ?answer ?allowed-values)) do
    (printout t ?question)
    (bind ?answer (read))
    (if (lexemep ?answer)
    then (bind ?answer (lowcase ?answer))))  ?answer)
;*********************************************************
;*****Questions Prostate Symptoms **************************
;*********************************************************
(defrule Questions_Prostate  "ask-question"
(initial-fact)
=>
(printout  t "Question About Prostate "  t)
```

(bind ?pass_urine (ask-question " When you want to pass urine, is there a delay before you start(yes/no)? " yes no) )

(assert (pass_urine ?pass_urine))

(bind ?flow (ask-question " When you pass urine, do you find your flow stops and starts(yes/no)? " yes no) )

(assert (flow ?flow))

**……..**

## 2. PROSTATE DISEASES DIAGNOSIS

## PROSTATE FUNCTION

```
(deffunction readdatafacts (?a)
    (while  (bind ?i (str-index "," ?a))
       (bind ?a (str-cat (sub-string 1 (- ?i 1) ?a) " " (sub-string (+ ?i 1) (str-length ?a) ?a)))
     )
    (bind ?a (explode$ ?a))
    (bind ?i (assert (luts
                    (age (0 0.1) (100 0.1))
                    (haematuria (1 0.5) (2 0.5))
                    (haemo_spermia(1 0.5) (2 0.5))
                    (painful_ejaculation (1 0.5) (2 0.5))
                    (fever (1 0.5) (2 0.5))
                    (chills (1 0.5) (2 0.5))
                    (bone_pain (1 0.5) (2 0.5))
                    (perineal_pain (1 0.5) (2 0.5))
                    (big (1 0.5) (2 0.5))
                    (painful_DRE (1 0.5) (2 0.5))
                    (stony_hard_DRE (1 0.5) (2 0.5))
                    (pyuria (1 0.5) (2 0.5))
                    (haematuria1 (1 0.5) (2 0.5))
                    (PsA (0 0.5) (100 0.5))
```

```
                )
            )
    )
    ;(bind ?t (nth$ 16 ?a))
    ;(if (numberp ?t) then
     ;(if (= ?t 1) then
       ;  (bind ?i (modify ?i (PCA yes))))
     ;(if (= ?t 2) then
        ; (bind ?i (modify ?i (AP yes))))
     ;(if (= ?t 3) then
         ;(bind ?i (modify ?i (BHP yes))))

    )


    (bind ?t (nth$ 1 ?a))
    (if (numberp ?t) then
     (bind ?i (modify ?i (age (create-fuzzy-value fz_age (?t 0) (?t 1) (?t 0)))))
    )

;    (bind ?t (nth$ 2 ?a))
;    (if (numberp ?t) then
;     (bind ?i (modify ?i (sex (create-fuzzy-value fz_sex (?t 0) (?t ;1) (?t 0)))))
;    )
```

```
    (bind ?t (nth$ 2 ?a))

    (if (numberp ?t) then

        (bind ?i (modify ?i (haematuria (create-fuzzy-value fz_haematuria (?t 0) (?t 1) (?t 0)))))

    )

    (bind ?t (nth$ 3 ?a))

    (if (numberp ?t) then

        (bind ?i (modify ?i (haemo_spermia (create-fuzzy-value fz_haematuria (?t 0) (?t 1) (?t 0)))))

    (bind ?t (nth$ 5 ?a))

    (if (numberp ?t) then

        (bind ?i (modify ?i (fever (create-fuzzy-value fz_fever (?t 0) (?t 1) (?t 0)))))

    )
```

**……..**

**3. WEKA RULES**

```
;*****************************************
; Bad prognosis rules
;*****************************************
(defglobal ?*out* = 0)
(defrule R_1
 (declare (CF 0.9))
 (fever yes)
 =>
  (assert (PROSTATITIS yes))
)
(defrule R_2
 (declare (CF 0.2))
 (and (fever no)(GDRENLARGED yes))
 =>
  (assert (BPH yes))
)

(defrule R_3
 (declare (CF 0.3))
 (and(fever no)(GDRENLARGED no)(PSA  normal))
 =>
  (assert (PCA yes))
)
```

```
(defrule R_4
 (declare (CF 0.1))
 (and(fever no)(GDRENLARGED no)(PSA high))
 =>
  (assert (PCA yes))
)
(defrule R_5
 (declare (CF 0.2))
 (and (fever no)(GDRENLARGED no)(PSA medium)(age middle))
 =>
  (assert (BPH yes))
```

**……..**

**APPENDIX IV**

*PARTA OF EXPERIMENTAL RESULTS AND FINAL HIROFILOS II OUTPUT*

| *AGE* | *LUTS* | *GHAEMATURIA* | *HEMOSPERMIA* | *PAIN EJAC* | *FEVER* | *CHILLS* | *BONE PAIN* | *PERINEAL PAIN* | *DRE: ENLARGED* | *DRE: PAINFUL* | *DRE: STONY/HARD* | *Ur. An. : PYURIA* | *Ur. An. : HAEMATURIA* | *PSA < 4* | *PSA : 4-10* | *PSA > 10* | *EXPERT DIAGNOSIS* | *HIROFILOS I* | *HIROFILOS II* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 83 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | **BPH** | **BPH** | **BPH** |
| 75 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | **BPH** | **BPH** | **Pca** |
| 70 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | **BPH** | **BPH** | **BPH** |
| 42 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | **PROSTATITIS** | **PROSTATITIS** | **PROSTATITIS** |
| 67 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | **BPH** | **BPH** | **BPH** |
| 47 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | **PROSTATITIS** | **PROSTATITIS** | **PROSTATITIS** |
| 74 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | **BPH** | **BPH** | **BPH** |
| 58 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | **BPH** | **BPH** | **BPH** |
| 68 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | **BPH** | **BPH** | **BPH** |
| 73 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | **BPH** | **PROSTATITIS** | **BPH** |
| 64 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | **BPH** | **BPH** | **BPH** |
| 82 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | **Pca** | **Pca** | **Pca** |
| 69 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | **BPH** | **BPH** | **BPH** |
| 59 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | **BPH** | **BPH** | **BPH** |
| 69 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | **BPH** | **PROST** | **BPH** |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | **ATITIS** | |
| 69 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | **BPH** | **BPH** | **BPH** |
| 70 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | **BPH** | **BPH** | **BPH** |
| 73 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | **Pca** | **Pca** | **Pca** |
| 77 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | **BPH** | **BPH** | **BPH** |
| 63 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | **Pca** | **BPH** | **Pca** |
| 86 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | **Pca** | **Pca** | **Pca** |
| | | | | | | | | | | | | | | | | | **PROST** | |
| 77 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | **Pca** | **ATITIS** | **Pca** |
| 59 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | **Pca** | **BPH** | **Pca** |

Histor

**Using Machine Learning Techniques to Improve the Behavior of a Medical Decision Support System**

Abstract: *Machine Learning (ML) provides methods, techniques, and tools that can help solving diagnostic and prognostic problems in a variety of medical domains. ML is being used for the analysis of the importance of clinical parameters and their combinations for prognosis, e.g. prediction of disease progression, extraction of medical knowledge for outcome research, therapy planning and support, and for the overall patient management. ML is also being used for data analysis, such as detection of regularities in the data by appropriately dealing with imperfect data, interpretation of continuous data used in the Intensive Care Unit, and intelligent alarming resulting in effective and efficient monitoring. It is argued that the successful implementation of ML methods can help the integration of computer-based systems in the healthcare environment providing opportunities to facilitate and enhance the work of medical experts and ultimately to improve the efficiency and quality of medical care. and in our research we use (ML) for diagnosis prostate gland diseases.*

*Prostate gland diseases, including cancer are estimated to be one of the leading causes of male death worldwide and its management is based on guidelines regarding diagnosis, evaluation, treatment and continuing care. In this study a fuzzy expert system for diagnosing, and learning purpose of the prostate diseases is described. HIROFILOS I is a fuzzy expert system for diagnosis and treatment of prostate diseases according to symptoms that are realized in one patient and usually recorded through his clinical examination as well as specific test results. The user-friendly proposed intelligent system is accommodated on a hospital web page for use as a decision support system for resident doctors, as an educational tool for medical students, as well as, an introductory advisory tool for interested patients. It is based on knowledge representation provided from urology experts in combination with rich bibliographic search and study ratified with statistical results from clinical practice.*

*Preliminary experimental results on a real patient hospital database provide an acceptable performance that can be improved using more than one computational intelligence approaches in the future.*

*Prostate gland diseases, including cancer, are estimated to be of the leading causes of male deaths worldwide and their management are based on clinical practice guidelines regarding diagnosis and continuing care. HIROFILOS-II is a prototype hybrid intelligent system for diagnosis and treatment of all prostate diseases based on symptoms and test results from patient health records. It is in contrast to existing efforts that deal with only prostate cancer. The main part of HIROFILOS-II is constructed by extracting rules from patient records via machine learning techniques and then manually transforming them into fuzzy rules. The system comprises crisp as well as fuzzy rules organized in modules. Experimental results show more than satisfactory performance of the system. The machine learning component of the system, which operates off-line, can be periodically used for rule updating, given that enough new patient records have been added to the database.*

**Key-Words:** - *Prostate disease, , urology, medical expert system, fuzzy logic*.