

## The potential of cancer screening programmes in europe

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Medicine today is seeing very rapid development of new technologies for the prevention, treatment and diagnosis of disease. Decision makers in the health services and health care professionals have to make choices and define strategies on the basis of criteria of safety, efficacy and benefit. The National Health agencies evaluate the various strategies, produce a summary of available information, and disseminate their conclusions to all partners involved in health care. Their role is to provide assistance with the individual and collective decision making process:

- they keep the public authorities informed of the state of scientific knowledge, its implication for medicine, organisation and financing, and the impact on matters of public health;
- they help health care establishments provide the best response to patient's needs in order to improve health care;
- they help health professionals define and implement the best strategies for diagnosis and treatment in line with the prerequisites.

They fulfil their mission in implementing national and European programmes of action against cancer.

### CANCER SCREENING PROGRAMMES: THEORETICAL AND POLITICAL ISSUES

For all the countries around the world combating cancer is a high priority. Today approximately one European in four, nearly one million per annum, will die of cancer. The cost of this is enormous, both in human terms for cancer patients and their families and in terms of the resources consumed by the diagnosis, treatment, and care of this disease. Evaluation and monitoring of cancer screening programmes are the roles of these National agencies and of course of the international organisations like the commission of the European communities, the International agency for research on cancer, WHO, European network of cancer registries, Europe against cancer-European commission. The national screening units have developed a clear vision for the future:

"Saving lives, reducing inequalities, and building the nation's health by leading the delivery of screening programmes, uncompromising in their quality and trusted by the communities they serve"

The aim of this paper is to provide information from different health organisations to set appropriate policies and quality control measures, provide sufficient guidance

and monitoring to ensure the overall safety, efficiency and benefits of the cancer screening programmes already implemented in Europe. In 1968, Wilson and Jungner of the World Health Organisation developed ten principles that should govern a national screening programme.

These are:

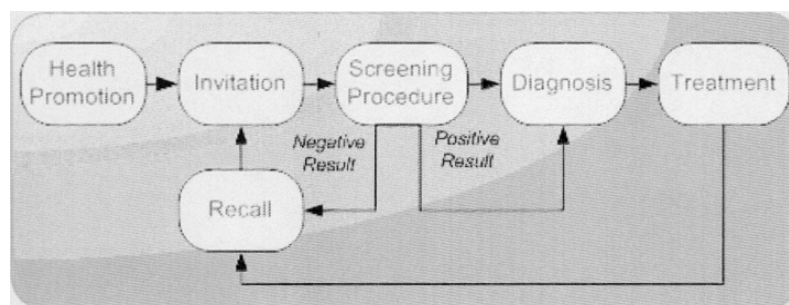
1. The condition is an important health problem
2. Its natural history is well understood
3. It is recognisable at an early stage
4. Treatment is better at an early stage
5. A suitable test exists
6. An acceptable test exists
7. Adequate facilities exist to cope with abnormalities detected
8. Screening is done at repeated intervals when the onset is insidious
9. The chance of harm is less than the chance of benefit
10. The cost is balanced against benefit

### WHAT IS SCREENING?

'Screening is a health service in which members of a defined population, who either do not necessarily perceive they are at risk of, or are already affected by a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications'. The aim of screening is to reduce the number of people suffering and/or dying from a specified health condition. It reduces the risk of developing or dying from a disease, but is not a guarantee of prevention, or of diagnosis and cure. As screening has benefits, costs, and harms, there is an ethical obligation to minimise harm and the overall benefits should outweigh any harm that result from screening. Screening refers not only to the initial test but also the sequence of events that comprise the screening pathway. All steps in the screening pathway must be undertaken to a high standard to ensure that the benefits outweigh the risks.

### THE SCREENING PATHWAY

In order for a screening programme to be successful, a coordinated approach is required. The essentials of such an approach include clear lines of accountability, high



quality service provision, effective monitoring of defined policy and quality standards, the timely availability and appropriate integration of screening services with diagnostic and treatment services, and high levels of programme enrolment and participation. In addition, it is important to identify priority groups who are most likely to benefit from screening and to ensure that the programme is accessible to these groups.

### THE EUROPEAN DIMENSION OF CANCER

Some 1,594,379 new cases were recorded in the fifteen Member States in 1997. The situation in the new Member States is expected to be very similar to the present situation in the European Union. The most frequent cancers in the European Union are colorectal, breast, lung, prostate, bladder, and stomach cancer, which, together, made up 59% of all new cancer cases. In 1997, the cancers responsible for the most deaths were lung, colorectal, breast, stomach, prostate cancer and pancreas cancer, which made up 57% of all cancer deaths. These figures explain why Europe is engaged in the global battle against this disease.

### TRANSLATING SCIENTIFIC ADVICE INTO LEGISLATION

Public health aims to prevent disease at population level and thus reduce the burden of disease for individuals and for society as a whole. While primary prevention (such as through tobacco control legislation) aims to reduce the incidence of cancer by avoiding exposure to carcinogens, secondary prevention aims to reduce mortality by the early detection of cancer through screening of the population at risk from carcinogens. Well-managed population screening should be more effective than individual screening on demand, and is therefore a key instrument of prevention that also needs to have a science-based, cost-effective approach, built on best practice.

### CANCER SCREENING FOR BREAST, CERVICAL AND COLORECTAL CANCER

Since the beginning of Europe against Cancer, clinical trials of specific screening methods have been shown to be effective for three different cancers: breast cancer, colorectal cancer and cervical cancer. For example, each

year breast cancer is diagnosed in about 220,000 European women and kills around 75,000. Estimates suggest, however, that the lives of about 25,000 women could be saved if best practice of screening was available to all women in the European Union.

In 1999, the Advisory Committee on Cancer Prevention prepared recommendations on cancer screening in the European Union. The Committee reviewed the scientific literature and analysed the experience from the different screening networks established under the Europe against Cancer programme. Based on the most up-to-date science, established a set of general principles for best practice in cancer screening and made specific recommendations for the implementation of mammography screening for breast cancer, pap smear screening for cervical cancer, and faecal occult blood testing for colorectal cancer.

A recommendation on screening with the PSA-test for prostate cancer could not be made at that time, as this depends on the outcomes of large international studies in the USA as well as in Europe, which are expected to become available in 2008.

### EXAMPLES OF SCREENING PROGRAMMES

#### The NHS cancer breast screening programme

The programme was set up by the Department of Health in 1988.

#### *What is breast screening?*

Breast screening is a method to detect breast cancer at a very early stage.

Mammograms are breast x-rays. When women have a mammogram, the radiographer who takes the x-ray will place each breast in turn between two plates on the x-ray machine. The plates hold the breast firmly for a few seconds while the pictures are taken. Many women find this uncomfortable; a few find it painful. It does not harm the breasts.

Mammographies...

- can detect tissue changes in the breast before anything can be seen or felt. In most cases, any changes detected will not be cancer.
- are particularly effective in women over 50 years of age who have mammograms every two years.

- can detect about 75 to 90% of all unsuspected cancers. However, in some cases an x-ray may indicate that something is not quite right when, in fact, all is well (false positive result). Or an x-ray may fail to pick up a cancer (false negative result).
- cannot prevent breast cancer, and cannot always prevent death from breast cancer. They can only detect breast cancer - but early detection means early treatment and a better chance of a successful outcome.
- are relatively safe because only very small amounts of radiation are used.

### **What does the NHS Breast Screening Programme do?**

The NHS Breast Screening Programme provides free breast screening every three years for all women in the UK aged 50 and over. Around one-and-a-half million women are now screened in the UK each year. Women aged between 50 and 64 are routinely invited for breast screening every three years, and work is being carried out to extend the programme to women up to and including the age of 70 by 2004. Because the programme is a rolling one that invites women from GP practices in turn, not every woman will receive an invitation as soon as she is 50. But she will receive her first invitation before her 53rd birthday. Once women reach the upper age limit for routine invitations for breast screening, they are encouraged to make their own appointment. The NHS Breast Screening Programme is an effective part of the UK's efforts to reduce the death toll from breast cancer. In September 2000, the first research was published which demonstrated that the screening programme has lowered mortality rates from breast cancer in the 55-69 age group. It is estimated that the programme is on course to save 1,250 lives per year (25 per cent reduction in mortality) by the year 2010. *How is the programme organised?*

There are over 90 breast screening units across the UK, each currently inviting an average population of around 45,000 women. Women are invited to a specialised screening unit, which can either be mobile, hospital based, or permanently based in another convenient location such as a shopping centre. The NHS Breast Screening Programme is nationally coordinated. It sets national standards that are monitored through a national quality assurance network. For England, there is a national coordination office, based in Sheffield, and an advisory committee that oversees the programme and reports to government ministers. The programme was commended as a "model service" in the Health Select Committee's third report into breast cancer services in July 1995.

### **How much does the programme cost?**

In England, the budget for the breast-screening programme, including the actual cost of screening is approximately £52 million. This works out at about £30 per woman invited or £40 per woman screened.

### **How will the programme develop in the future?**

The NHS Cancer Plan, published by the Department of Health in September 2000, sets out future developments in the NHS Breast Screening Programme. The programme will be extended so that women up to and including the age of 70 receive routine invitations for screening by the end of 2004. By 2003 all women will have two views of the breast taken at every screen instead of just at the first screen as at present - one from above (craniocaudal) and one into the armpit diagonally across the breast (mediolateral). Research has shown that this could increase small cancer detection rates by up to 43 per cent. These changes to the breast-screening programme will entail the biggest expansion to the programme since it was launched.

### **Why are women under 50 not invited?**

Women under 50 are not offered routine screening. They can ask their GP to refer them to a hospital breast clinic if they are concerned about a specific breast problem or otherwise worried about the risk of breast cancer. This is not part of the NHS Breast Screening Programme.

### **Does breast screening save lives?**

The programme in the UK has screened more than 14 million women and has detected over 80,000 cancers. Research published in the British Medical Journal in September 2000 demonstrated that the NHS Breast Screening Programme is saving at least 300 lives per year. That figure is set to rise to 1,250 by 2010. By 2010 the effect of the screening programme, combined with improvements in treatment and other factors (including cohort effects), could result in up to a halving of the breast cancer death rate in women aged 55 - 69 from that seen in 1990.

The World Health Organisation's International Agency for Research on Cancer (IARC) concluded that mammography screening for breast cancer reduces mortality. The IARC working group, comprising 24 experts from 11 countries, evaluated all the available evidence on breast screening and determined that there is a 35 per cent reduction in mortality from breast cancer among screened women aged 50 - 69 years old. This means that out of every 500 women screened, one life will be saved.

### **The NHS cervical screening programme**

The NHS Cervical Screening Programme was set up in 1988 when the Department of Health instructed all health authorities to introduce computerised call-recall systems and to meet certain quality standards. The programme screens almost four million women in England each year. Of the 3.8 million women in the target age group screened in 2001-02, 2.7 million were tested following an invitation and 1.1 million were screened opportunistically at the suggestion of the smear taker or of the woman herself. For clinical reasons some women have more than

one smear test during the course of a year and an estimated 4.4 million smears were examined by pathology laboratories during 2001-02. Of the 13.8 million women aged 25-64 eligible for cervical screening in 2001-02, 81.6 per cent had been screened within the previous five years. More than 100,000 people are involved in cervical screening. They include the doctors and nurses who take the smears in GP surgeries and community clinics, the laboratory staff who review the smears and the people who run the computer systems...

### **What is cervical screening?**

Cervical screening is not a test for cancer. It is a method of preventing cancer by detecting and treating early abnormalities that, if left untreated, could lead to cancer in a woman's cervix (the neck of the womb). The first stage in cervical screening is either a smear test or Liquid based Cytology (LBC). A sample of cells is taken from the cervix for analysis. A doctor or nurse inserts an instrument (a speculum) to open the woman's vagina and uses a spatula to sweep around the cervix. Most women consider the procedure to be only mildly uncomfortable. Early detection and treatment can prevent 80 to 90 per cent of cancers developing but like other screening tests, it is not perfect. It may not always detect early cell changes that could lead to cancer.

### **What is a smear test?**

The sample of cells is 'smeared' on to a slide that is sent to a laboratory for examination under a microscope.

### **What is LBC?**

Liquid based cytology (LBC) is a new way of preparing cervical samples for examination in the laboratory. The sample is collected in a similar way to the conventional smear, using a special device (spatula) that brushes cells from the neck of the womb. Rather than smearing the sample onto a microscope slide as happens with the conventional smear, the head of the spatula, where the cells are lodged, is broken off into a small glass vial containing preservative fluid, or rinsed directly into the preservative fluid. The sample is sent to the laboratory where it is spun and treated to remove obscuring material, for example mucus or pus, and a random sample of the remaining cells is taken. A thin layer of the cells is deposited onto a slide. The slide is examined in the usual way under a microscope by a cytologist. Computer-assisted detection of cervical abnormalities is a possibility for the future.

### **Who is eligible for cervical screening?**

All women between the ages of 25 and 64 are eligible for a free cervical smear test every three to five years. In the light of new evidence<sup>1</sup> the NHS Cervical Screening Programme will now be implementing screening at different intervals depending on age.

Age group (years)	Frequency of screening
25	First invitation
25 - 49	3 yearly
50 - 64	5 yearly
65+	Only screen those who have not been screened since age 50 or have had recent abnormal tests

### **Why are women under 25 and women over 65 not invited?**

Cervical cancer is rare in women under 20. Teenagers' bodies, particularly the cervix, are still developing, which means young women may get an abnormal smear result when there is nothing wrong. This could lead to unnecessary treatment so screening young women might do more harm than good. Under the age of 25 years, invasive cancer is extremely rare, but changes in the cervix are common. Although lesions treated in very young women may prevent cancers from developing many years later, the evidence suggests that screening could start at age 25. Lesions that are destined to progress will still be screen-detectable and those that would regress will no longer be a source of anxiety. Younger women will not have to undergo unnecessary investigations and treatments. Any woman under 25 who is concerned about her risk of developing cervical cancer or her sexual health generally, should contact her GP or Genito-Urinary Medicine (GUM) clinic. Women aged 65 and over who have had three consecutive negative smears are taken out of the call-recall system. The natural history and progression of cervical cancer means it is highly unlikely that such women will go on to develop the disease. Women aged 65 and over who have never had a smear are entitled to a test.

### **What about women who are not sexually active?**

The NHS Cervical Screening Programme invites all women between the ages of 25 and 64 for cervical screening. But if a woman has never been sexually active with a man, then the research evidence shows that her chance of developing cervical cancer is very low indeed. We do not say no risk, only very low risk. In these circumstances, a woman might choose to decline the invitation for cervical screening on this occasion. If a woman is not currently sexually active but has had male partners in the past, then we would recommend that she continues screening.

### **How much does the programme cost and how is it funded?**

Cervical screening - including the cost of treating cervical abnormalities - has been estimated to cost around £150 million a year in England, or about £37.50 per woman screened. Primary Care Trusts commission cervical screening from the overall allocation they receive from the Department of Health.

## The ANAES and NHS proposals for screening colorectal cancer

### *How many people get colorectal cancer?*

Colorectal cancer is one of the most common cancers in France and other EU countries. 33,500 new cases of colorectal cancer are diagnosed and there are about 16,000 from the disease. Screening is based on examination of the colon and rectum to detect cancers at an early stage of growth as well as any adenomatous polyps.

### *Which screening tests?*

Barium enema is an unsatisfactory test in terms of test performance. It is invasive, requires full bowel preparation, and does not allow removal or biopsy of lesion seen. It is not used as a screening test.

Flexible sigmoidoscopy can detect 80% of colorectal cancers as it examines the whole of the left colon and rectum. It is rarely performed in France. A strategy of providing single flexible sigmoidoscopy for adults aged 55-65 years with the aim of detecting adenomas may be cost effective. A UK multicentre trial of this strategy for population screening is currently under evaluation. Although flexible sigmoidoscopy is more expensive than rigid sigmoidoscopy, it is generally more acceptable to patients (it is less uncomfortable) and has much higher yield than the rigid instrument. Many nurses are now trained to perform flexible sigmoidoscopy, making potential screening programmes using this technique more cost effective. In a population screening programme, uptake of the offer of the screening test is crucial. Uptake is likely to be around 45%, and, of these, 6% will subsequently need full colonoscopy.

Colonoscopy is the gold standard technique for examination of the colon and rectum, but its expense, the need for full bowel preparation and sedation, and the small risk of perforation of the colon make it unacceptable for population screening. Colonoscopy is, however, the investigation of choice for screening high-risk patients (those at risk of hereditary non-polyposis colon cancer or with longstanding ulcerative colitis). In France, its use as a mass screening test is controversial to a non-negligible risk of complication.

Faecal occult blood tests are the most extensively studied screening tests for colorectal cancer. These tests detect haematin from partially digested blood in the stool. Their overall sensitivity for colorectal neoplasia is only 50-60%, though their specificity is high. In screening studies of faecal occult blood tests, individuals are invited to take two samples from each of three consecutive stools. Compliance is around 50-60%, but with population education this might be improved. Individuals with more than four out of six positive tests (about 2% of participants) need colonoscopy. Several large randomised studies have shown that screening with faecal occult blood testing is feasible, and two studies have shown that such screening reduces the mortality from colorectal cancer. In a study in

Nottingham, for every 100 individuals with a positive test result, 12 had cancer and 23 had adenomatous polyps. The cancers detected at screening tended to be at an earlier stage than those presenting symptomatically (Dukes's A classification: 26% screen detected vs 11% in controls). The disadvantage of screening with faecal occult bloods is its relatively low sensitivity; a third to a half of cancers will be missed on each round of screening. The Nottingham data suggest that screening every two years detects only 72% of cancers. This could be improved by testing annually and using more sensitive immunologically based faecal occult blood tests.

Virtual colonoscopy also called CT colography is a new technique for imaging the colon which uses a helical CT scan and image processing by computer to produce 3D representation of the colon, simulating the images obtained by the colonoscopy. The sensitivity varies between 50% and 100% for polyps larger than 10mm, 38.5% and 82% for polyps between 5 and 10 mm, 0-59% for polyps smaller than 5mm. Specificity varies from 62 to 98% for polyps larger than 10 mm. The wide variations can be explained by the differences in the hardware and software used and the experience of the operator. Virtual colonoscopy is relatively non-invasive investigation that does not require an anaesthetic. But the patient has to undergo similar preparation to that used for colonoscopy. The main disadvantage is gastrointestinal side effects and discomfort caused by the need to ingest a large volume of solution. This technique is still at the development stage.

### *Who should be screened?*

Although about 20% of the population will develop adenomatous polyps, only 5% of these will develop colorectal cancer. This equates to a 1 in 20 lifetime risk for colorectal cancer. The cancer occurs most often in the age group 65-75 years, but for adenomas the peak incidence is in a slightly earlier age group (55-65 years). Thus population screening for colorectal cancer should target both these age groups. In addition, some people inherit a much higher susceptibility to colorectal cancer. Some inherit a well-recognised single gene disorder, such as familial adenomatous polyposis or hereditary non-polyposis colon cancer, whereas most inherit an undetermined genetic abnormality. These people tend to develop colorectal cancer before the age of 50, and therefore screening in this high-risk population needs to be tailored to each individual's risk pattern. They may also be at risk for cancers at other sites, and screening for ovarian, breast, and endometrial cancers may be appropriate in some of these cases. The advice of clinical geneticists in these cases can be invaluable.

### *Cost effectiveness of screening*

If screening for colorectal cancer is to be acceptable to healthcare providers it must be shown to be cost effective. Estimates of the cost of screening for colorectal cancer range from 1500 to 4500 per life-year saved,

depending on the screening technique used. The cost of using faecal occult blood testing would be the lowest, similar to estimates for breast cancer screening.

### Appropriateness of systemic screening for prostatic cancer by PSA

In France, the standardised incidence (per 100,000 inhabitants) of prostatic cancer ranges between 24.9 and 37.9. In Europe, the range is between 17.1 (Poland) and 74.7 (Sweden) 1992 data. Standardized mortality (per 100,000 inhabitants) is 16.7 in France while in Europe the range is between 11.9 (Poland) and 22.2 (Norway). In terms of prevalence, the only available data are derived from autopsy series in which histological prevalence ranges from 12% in the 40-49 age-bracket to 43% in patients over 80. In terms of life lost, the impact is much lower than that of the lung cancer or gastrointestinal cancers. Many risk factors have been suspected: familial, ethnics, history of vasectomy, diet, sex hormones, exercise, etc., none have been proved and at the current stage of knowledge it is not yet possible to provide any guidance on primary prevention. The development of prostatic cancer is androgen dependant. 95% are adenocarcinomas. Although 30-40% of men may have prostatic cancer, only 8% are likely to develop a clinically significant cancer and fewer than 5% are likely to die with it. Evidence in the literature on untreated prostatic cancer shows high survival rates at 5, 10, 15 years. A blood test to determine PSA concentration can identify a biological abnormality. In routine practice, there are problems of variation of results depending of the methods used. Modified PSA test have been proposed (PSA velocity test, PSA density test, age referenced PSA concentration, free PSA) but their use has not proven to be superior. Others test can be used to screen for prostatic cancer, such a digital rectal examination, and transrectal ultrasonography of the prostate. They have the same limitations as PSA with regard to true measurement of the prevalence of the disease.

### Which optimum strategy?

The most powerful strategy might be a combination of PSA and digital rectal examination, with a biopsy when one of the two tests is positive. However no optimum strategy has yet been defined. There are no randomised or case control studies that demonstrate that routine screening for prostatic cancer has a benefit in terms of specific mortality or quality of life. Various screening strategies are in progress in Canada, USA, and the EU. There is no definitive result; In addition to the WHO criteria, an analysis of the benefits of screening needs to include economic factors. Also evidence does not yet support population screening for prostate cancer. There is considerable demand for the PSA test amongst men worried about this disease. In response to this, some governments have introduced a PSA informed choice programme "Prostate cancer risk management (UK)". The key elements are the provision of high quality information for men reque-

sting the test. This should enable men to decide whether or not to have the test based on the available evidence about risks and benefits.

### IN CONCLUSION

Cancer screening for breast, cervical and colorectal cancer is effective. But there is a need for bench marking. Screening for cancer and the establishment of best practice still vary between states. The EU council recommendation on cancer screening aims to close the gap between differences in screening among the member states to achieve a similar reduction of cancer specific mortality in all member states by establishing general principles of best practice for cancer screening. The intention is to bring about a similar high level of health protection for those cancers where early detection is possible and efficient for all European citizens. In the proposal for the EC council recommendation on cancer screening, presented by the Commission in Brussels on May 05, 2003. The conclusions are:

Organised cancer screening should be offered to healthy people if the screening is proved to decrease disease-specific mortality and/or decrease the occurrence of advanced disease, if the benefits and risks are well known, and if the cost-effectiveness of the screening is acceptable.

At present the following screening tests meet such requirements:

- pap smear screening for cervical abnormalities starting at the latest by the age of 30 and definitely not before the age of 20,
- mammography screening for breast cancer in women aged 50-69 in accordance with European guidelines on quality assurance in mammography,
- faecal occult blood screening for colorectal cancer in men and women age 50-74.

Decisions on implementation of cancer screening programmes must be made as part of a general priority-setting exercise on the use of healthcare resources.

Other cancer screening tests are not yet recommended for EU-wide population-based cancer screening, although they already may be used in individual screening on demand. Such tests may provide individual benefits but at the same time may also lead to adverse effects for individuals (e.g. unfounded anxiety) and the public (e.g. additional financial burden). Recommendations for such tests cannot be made until they have been shown to have benefits such as reducing disease-specific mortality or improving survival.

Potentially promising screening tests currently being evaluated in randomised controlled trials, include:

- prostate-specific antigen (PSA) testing for prostate cancer,
- mammography screening for women aged 40-49 for breast cancer,
- immunological Faecal Occult Blood Testing (FOBT) for colorectal cancer,

- flexible colonoscopy for colorectal cancer.

Once the effectiveness of a new screening test has been demonstrated, evaluation of modified testing methods may be possible using intermediate/surrogate endpoints, if the positive predictive value of such endpoints is sufficiently established. Some examples of screening methods that fall into this category are listed below:

- any novel alternative tests for faecal occult blood,
- liquid-based cervical cytology,
- testing for high risk human papilloma virus (HPV) infection,
- other novel methods for the preparation or interpretation of cervical specimens.

Any screening test which has been demonstrated to be effective should be offered on a population basis only in organised screening programmes, with quality assurance at all levels and full information about the benefits and risks.

Note: This paper is an educational article summarizing a large part of the information published by the Council of the European Union, the NHS, the ANAES, the NZ Ministry of Health and the BMJ.

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