



Where is Research Going? What are We Doing About it?

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Where is Research Going?

Prefix

Advances in genetics are reaching out into virtually every area of modern medicine. They will affect every section of our increasingly diverse, multi-cultural society and we will all have to adapt to this new knowledge as we come to realise the potential for altering the balance between health and disease in an increasing number of cases and hitherto intractable conditions become amenable to treatment and eventually to cure.

One common thread binds genetics in all its diversity together – the fact that it is the patient who is the sole involuntary partner in this process of discovery and development.

This conference highlighted the importance of patient and family input to the process of research and to the implementation of its outcomes. It brought together representatives of patient groups supporting those with rare conditions and with common ones. Regulators, clinicians, industry and academia contributed to lively and wide ranging discussions which this report seeks to capture and reflect. Inevitably it is partial and subjective. Occasionally it may misrepresent points attributed to speakers and if this is the case I apologise and accept the responsibility for the error.

One thing is certain – the onward march of new genetic knowledge has fantastic potential to improve the health of millions of European Citizens and will not be realised unless patients are full and active partners in achieving this.

Alastair Kent

What are We Doing About it?

President
EAGS

EAGS open meeting and conference

Where is research going?

What are we doing about it?

Science and the interface

Research, Stem Cells and Patients
Alastair Kent, Director, Genetic Interest Group

Gene therapy – what is it and how close are we to being able to use it in practice?
Lorna Layward, Director of Research, Cystic Fibrosis Trust.

Biotechnology as a route to new treatments. Beta-Interferon, a case study of the transfer from basic science to a new medicine.
Professor Michel Revel, Department of Molecular Genetics, Weizmann Institute of Science; Chief Scientist, InterPharm Ltd, Israel

Orphan medicinal products one year on. How are the regulations working in practice?
Dr Agnes Saint-Raymond, EMEA

Where is Research Going?

Parallel workshops

- 1 Equity of access to genetic services in a multi-ethnic Europe.
Workshop leader Dr Aamra Darr, The Open University.
- 2 Access to new treatments – making the system work for patients.
Workshop Leader: Andrea Rappagliosi, Vice President, Health Policy and Government Relations, Serono

Parallel workshops repeated

EAGS open meeting and conference

DNA diagnostics, looking to the future.

A Joint EAGS/European diagnostics manufacturers association (EDMA) seminar

Better advocacy for patient organisations in EU Political arenas
Ysbrand Poortman and Cees Smit EPPOSI

The 6th Framework Programme – Guidance on the Preparation of Expressions of Interest.
Elmer Nimmegern. DG Research, European Commission

Gen-Ed
Professor Rodney Harris. University of Manchester and Professor Irma Nipper. University of Munster.

What are We Doing About it?

What do clinicians need from a diagnostic laboratory?
Prof Domenico Coviello, Clinical Geneticist, Milan

DNA Based Diagnostics: Issues in monogenic and common complex diseases and pharmacogenetic.
Prof Klaus Lindpainter, Head of Roche Genetics, F Hofmann-La Roche Ltd, Switzerland.

Providing a service, an industry perspective.
Dr Erik Tambuyzer, Vice-President, Corporate Affairs Europe, Genzyme Corporation, Belgium.

Measuring and maintaining quality in DNA diagnostic laboratories.
Dr Rob Elles, Head of DNA laboratory, St Mary's Hospital, Manchester.

The need for fast and accurate diagnosis – the patient perspective.
Ysbrand Poortman, (Formerly Executive Director) VSOP, Netherlands.

Concluding remarks
John Place, Executive Director, EDMA, Belgium.

Where is Research Going?

Research, Stem Cells and Patients

Alastair Kent

Director, Genetic Interest Group

Introduction

Stem cells can be derived from a variety of sources in the human body, including from the early embryo (pre-implementation), the fetus (post abortion) from cord blood and from adult tissues. Wherever they derive from they represent a potential source of new treatments for a wide range of disorders which are currently either incurable or intractable. Recent research has indicated that stem cells from all the above sources may have a role to play in developing these cures, but our present knowledge is insufficiently developed to be able to establish which route, if any, will prove to be most likely to deliver.

A controversial area for investigation

Some forms of treatment using stem cells have been available for many years and are now relatively uncontroversial. Bone marrow transplants have been used with great success to treat a range of conditions.

A degree of controversy attaches to some other types of therapy. For example, the recent use of pre-implantation genetic diagnosis to secure tissue compatible siblings for children affected by Fanconi's Anaemia and Thalassaemia, allowing cord blood stem cells to be extracted for therapeutic use, has attracted considerable media

What are We Doing About it?

attention and generated public discussion. Whilst views vary, the general consensus seems to be in favour of allowing this given the potential for health gain in those countries where preimplantation genetic diagnosis is permitted.

Most controversial of all is the use of stem cells derived from embryos. Paradoxically this may be the most promising line of research due to the toti-potency of embryonic stem cells. So far this is not thought to be the case with stem cells from other sources.

Potential Application

Research using stem cells is at the very beginning of the process from "bright idea" to useful intervention. Nevertheless there are hopeful signs that may result in great progress, if the early findings can be followed through.

Stem cells are already being used for toxicity testing and for early stage efficacy studies of new therapeutic compounds.

Within 5-10 years it is possible that we will see stem cells used in cellular transplantation – especially into the pancreas, heart and muscles for treatment of diabetes, heart disease and muscle wasting disorders such as muscular dystrophy.

In the longer term we may see stem cell transplants being used to treat liver disease, kidney failure, neurological and auto-immune disorders because of their potential to replace cell types damaged or

Where is Research Going?

destroyed by the disease process. Such applications might help patients with:-

- Stroke
- Neurodegenerative disorders (e.g. Parkinson's, Alzheimer's)
- Diabetes
- Heart disease
- Muscle wasting disorders etc

Ethical Issues

Let us examine the hardest case first – the use of embryonic stem cells.

There are two potential sources of embryonic stem cells – “spare” embryos left over from invitro fertilisation procedures and cloned embryos from cell nuclear replacement techniques. Either source can produce stem cells, which can then be used to create immortal cell lines.

The source of these cell lines brings with it feelings of unease for some people. There is a deep-seated notion of “respect” for life, which in itself is important in ensuring that research is undertaken in an ethical context. However, when considering “respect” in this context, do we mean respect for the embryo, which is clearly unaware of its own existence or respect for the feelings of others? On one level there is the absolute position that all human life is equally important. This view would absolutely preclude the use of embryos in any form of research. If one is not absolutist, then the issue is when and where to draw the line.

What are We Doing About it?

Defining the limits to research requires one to weigh up the pros and cons – a cost/benefit analysis of the conditions under which research and development using embryos is to be either allowed or prohibited.

On the positive side there is agreement that research using embryonic stem cells is potentially important, possibly yielding substantial benefits in the treatment of a wide range of currently incurable diseases.

On the negative side, the research inevitably requires the destruction of a number of human embryos.

Respect for embryonic origin is required, but it is not absolute. We must also consider the desirability of the goal, the fact that the embryos are in the very early stages of development where there is a very high natural wastage and the observation that attachment seems to grow as all pregnancy develops. Perhaps the best notion of “respect” is the Kantian one of “wariness” – i.e. proceed with caution and consideration.

Regulations

Because of the sensitivities surrounding the origins of embryonic stem cells there is a need for a regulatory framework to define what is or is not to be allowed. Such a framework might include measures which take account of:-

- The seriousness of the condition
- A lack of other forms of effective treatment

Where is Research Going?

- The quality of the science proposed
- The competence of the centre seeking approved to do the work.
- Consent from the donors of the embryos

Once a cell line has been established it is clear that it is no longer an embryo and consequently the respect due diminishes. It is more a question of recognising their origin and of being sensitive to the feelings of the donors and societal sensitivities about the issue. Other than their origin, it is arguable that embryonic stem cell lines do not differ significantly from other cell lines used in research.

Subsidiarity

It is clear that there is no single view in the European Union about the appropriateness or otherwise of using embryos in research. Nor is harmonisation possible. Short of an outright ban, regulations would have to be either so draconian as to make it unworkable to attempt research, or so vague as to permit almost anything. The recent difficulty of achieving consensus experienced by the European Parliament Special Temporary Committee on Genetics is a case in point. If agreement on what is arguably less contentious proved impossible, it would be doubly difficult in this area.

Europe demonstrates a moral plurality existing legislation at a national level allows for this to be recognised and respected. When research moves on and treatments using stem cells derived from embryos become available, there will be pressure from those wishing to benefit, for legislation to be enacted in countries where this is not currently possible to allow access. Otherwise the free

What are We Doing About it?

movement of citizens will allow those with the resources to travel in order to benefit – with a demand for payment being made on their home state's health care system – potentially creating a system of rationing based on wealth and/or ability to organise oneself, not clinical need.

Conclusion

Research using embryonic stem cells is showing great promise for relieving many severe and complex disorders. Resolving the ethical issues associated with the research has proved challenging but a “modus vivendi” seems to have been reached. As and when treatments emerge, new issues will be raised that will need to be resolved if European Citizens are to benefit from access to an equitable, needs based health care system.

Gene therapy – What is it and how close are we to being able to use it in practice?

Lorna Layward: Director of Research. Cystic Fibrosis Trust.

Introduction

“Gene therapy” refers to the transfer of new genetic material into the cells of individuals affected by a serious health problem with resulting therapeutic benefit for that individual. It does not involve the germ line and the benefits are not transmitted either to the next generation or the population as a whole. Germ line modification is currently not permitted on both ethical and scientific grounds.

Where is Research Going?

Originally gene therapy was conceived as the correction of a faulty gene by gene transfer – adding whole new genes to the affected individual. Now, thinking is directed more to gene correction - changing the mutation causing the particular problem – using a gene as part of a therapeutic agent.

Research approaches

In autosomal recessive disorders, understanding of the gene and the gene product will theoretically enable treatment of the disease at the level of the underlying cause. This is likely to prove better and more effective than symptomatic relief.

The challenges facing researchers are to find the right vector and to get the vector to transport the gene into the appropriate cells in the human body. Once in the cell there is a further difficulty, that of getting the “new” genetic material incorporated and functioning – producing the relevant protein and overcoming the body’s defences to the product and the vector.

A range of viruses have been used as potential delivery systems – adenovirus, adeno-associated virus, lentivirus (e.g. HIV). Experiments have also tried naked DNA and DNA in fatty globules. Viruses are potentially the most promising because of their ability to enter the cell and incorporate their DNA into that of the host. The research challenge is to modify the process so the virus is not self replicating and also so that it contains the desired genetic information for incorporation into the host’s genome – a simple enough concept, but very difficult to achieve in practice.

What are We Doing About it?

The Ideal Vector

An ideal vector would display the following characteristics: –

- Capable of being produced in high concentrations
- Stable
- Tissue specific
- Capable of having its expression regulated
- Non-immunogenic
- Demonstrating incorporation into the genome
- Reversible in its effect

No vector has yet been developed that does all of these.

Potential disease targets

All types of genetic disorders – monogenic, complex (polygenic) and possibly even infectious disease

Progress to date

Gene therapy has been used to great effect in the treatment of ADA deficiency – AFA-SCID and X linked SCID.

Gene therapy has also been attempted, but with no real progress to date in a range of other disorders including:–

- Mucopolysaccharide disease
- Familial hypocholesterolaemia

Where is Research Going?

- Cystic Fibrosis
- Haemophilia B (Factor IX deficiency)
- Thalassaemia
- Chronic Granulomatous Disease

Whilst the research has given much new knowledge, difficulties are being experienced in introducing enough genes and in producing an effect other than a short lived one. Production of the gene product (the protein) has also not been reliably achieved in many cases, resulting in the absence of any clinically visible effects.

Clinical Trials

Gene therapy for cancer has dominated clinical trials attempted to date. 63% of trials undertaken have been for cancers and this trend is likely to continue for the foreseeable future. 12% of trials have been for monogenic disorders, with heart disease and infectious diseases an increasing proportion of the rest.

There is the danger that a lack of research funding for inherited monogenic disorders will squeeze these out of the programme. If this is not to happen, patient groups will need to be active in lobbying for their interests and securing a fair allocation of the available resources.

The whole field is still very experimental but clinical trials are giving positive results and providing pointers for future progress,

What are We Doing About it?

To date 3500+ people have participated in trials for a wide range of different diseases. 63% of these have been in the US and over 600 different trials have been carried out. Most of these have been either phase I or II – proof of concept and safety. In the EU, most of the work in this field has been in the UK, but the volume of experiments in other member states is rising.

Further issues

The provision of gene therapy is real, but there has been a tendency to exaggerate both the size and the speed of the delivery of benefits. This, combined with public anxiety about “promoting an ideal, not combating an end”, has led to a degree of cynicism in some quarters. This has harmed the interests of patients and also the scientists, clinicians and pharmaceutical interests which seek to develop this novel form of therapy.

There is a need to increase our knowledge, with the appropriate safeguards in place to prevent abuse and make the attainment of the possible therapeutic benefits a reality not a dream.

Where is Research Going?

Biotechnology as a route to New Treatments – Beta Interferon as a Case Study for the Transfer from Basic Science to a New Medicine.

Professor Michael Revel. Weizmann Institute of Science and InterPharm Ltd

Introduction

The use of genetics engineered into biotechnology as a route to therapies is a very new concept. Twenty-five years ago this area of R & D was as provocative and controversial as embryonic stem cells are today. Drug development, whether by conventional or biotechnological routes, is expensive and time consuming. Typically it can take 12 years and 200m+ Euros to move from basic science to a new medicine authorised and approved for use and available for patients who need it. Typically the process follows a number of steps:–

- Identification of the molecule
- Establishment of the mechanism of action
- Testing and development
- Clinical Trials
- Demonstration of Safety and Efficacy
- Market Authorisation
- Patient Benefit

Good basic science is the kick-starter for this process, but its successful completion requires collaboration between academia and industry.

What are We Doing About it?

New opportunities

The Human Genome Project has created a range of opportunities for generating solutions for many of the health problems affecting people today. These will come about by:–

- Creating new pharmaceutical products
- Developments in functional genomics
- The production of new diagnostic tests
- Achievement of gene therapy as a viable clinical therapy

Human gene products are already being used to produce new drugs for the treatment of serious diseases. Human insulin and human growth hormone are both now produced using the techniques of genetic engineering, avoiding potential problems associated with obtaining these molecules from human or animal sources.

Interferons are another very important class of drugs now available through progress in biotechnology – whether alpha-interferon for use in the treatment of cancer of hepatitis C or beta-interferon for MS and autoimmune disorders

How do interferons work?

Two modes of action have been identified for interferons. They can either have an anti-viral effect or an immunomodulatory effect. This latter property has been central to the development of treatments for Multiple Sclerosis (MS) where beta-interferon acts as a regulator of the immune system, which is damaged by the disease.

Where is Research Going?

Drug development

The challenge for science was to make beta-interferon in sufficient quantities for it to be a viable form of therapy in a form that was as similar as possible to the naturally occurring protein. This would avoid exposing patients to the risks associated with “natural” problems extracted from cadaverous sources, with the associated risks of HIV, CJD and hepatitis C.

Chinese Hamster Ovary Cells (CHO) were selected as a suitable baseline material. These were gradually modified to make them produce the human protein and the production scaled up to produce clinically significant quantities. (A genetically modified bacterium that was also used as an experimental model did not produce proteins sufficiently similar to the human molecules. There were also production problems compared with the CHO cells, which showed higher activity and a more potent product). The CHO cells released beta-interferon into the culture medium, allowing it to be harvested and purified.

The recombinant protein proved to be very stable, allowing it to be stored in a liquid form suitable for injections – science and technology coming together in a form that gives real patient benefit in the form of an appropriate and acceptable treatment regime which maximises the biological activity (and therapeutic benefit) of the drug.

What are We Doing About it?

Planning the Clinical Trials

This is a scientific challenge. Asking the right questions to enable determination of dosages and schedules and defining the end points to define success are central elements if important clinical questions are to be answered. Issues to be addressed are:-

- The long term efficiency of the treatment
- The dose regime over time
- The need for early vs. late treatment

Trial results revealed a gradual progression to a high level of relapse prevention if treatment using high doses is started early. The disease also showed less progression as measured by neurological involvement.

Complex diseases such as MS require objective measures to demonstrate real change. In MS trials MRI scans gave accurate measures of brain lesions, allowing estimates to be made of the brain damage prevented by the drug as compared with that which would have been anticipated – with better results in terms of prevention of disability, re-lapses etc.

Comparative studies provided the evidence to determine the most appropriate treatment regime. Clinical demonstrations of efficacy bear out laboratory predictions.

Where is Research Going?

Making the case for using the drug in Clinical Practice

Understanding the natural history of the disease (MS) makes it possible to calculate what would be expected in the absence of treatment. It allows the cost of delaying or denying treatment to be compared with the cost of providing it – as measured by the prevention of loss of function, retardation of the development of brain lesions and the consequent onset of disability – bearing in mind the one way nature of the disease and the fact that what is lost is not regained.

Basic Science to therapy

This process requires collaboration between all stakeholders – patients, academics and medians and industry - in order to determine:-

- The best molecule to use
- The best treatment regime
- The best manufacturing regime to produce the product (CHO or bacterial cells)

When these come together then biotechnology has shown itself to be a powerful vehicle for developing new therapies for the benefits of patients with serious, chronic and life threatening disorders.

What are We Doing About it?

Orphan Medicinal Products One Year On. How are the Regulations Working in Practice?

Dr Agnes Saint Raymond. EMEA

Introduction

Orphan designation is granted to medicinal products before marketing authorisation (the permission to put a new drug on the market) is given. It is available for products designed for conditions affecting fewer than 5 in 10,000 in the EU. The regulations are for all medicinal products, not just drugs. Orphan designation is available when the conditions for which the product will be used are life threatening or debilitating, where development costs are likely to be high relative to the potential size of the market or where the new products will provide a significant clinical benefit over an existing treatment.

Orphan Designation - incentives

Granting orphan designation brings significant benefits to the holder. The most important of these is the grant of 10 years of market exclusivity in the EU – unless another similar product for the same indication can show significant clinical superiority.

In addition, sponsors of orphan products are entitled to protocol assistance (advice from EMEA to help them plan the development of their product in ways that will generate evidence of safety and effectiveness likely to satisfy the regulatory committee). They have direct access to the centralised procedure – so their market authorisation, once granted, applies throughout the EU and they

Where is Research Going?

benefit from fee reduction and access to research funds available from the European Commission.

The Committee for Orphan Medicinal Products.

This is made up 21 members – one from each member state, three nominated by EMEA and uniquely, three representatives of patient groups. The Committee (known as COMP) is responsible for designation, for offering advice to the Commission on policy relating to orphan drugs and for international co-operation and collaboration with similar regulatory regimes elsewhere in the world.

Designation

In its first year of operation it was anticipated that there would be about 10 applications for orphan designation. In fact 70 were received!

To date, the committee, subsequently confirmed by the Commission, has granted over 100 designations. Two have been negative and over 50 applications have been withdrawn by the sponsor at some point in the application process. Many of the applications (approx. 50%) relate to rare types of cancer. Of these about 75% relate to both children and adults, whilst 25% are for children only diseases.

Interestingly, unlike applications for “non-orphan” disorders, where large companies are typically involved, in the case of orphan products the sponsors are often small organisations.

What are We Doing About it?

Withdrawals

Products are withdrawn during the procedure for various reasons eg failure to demonstrate that prevalence is below 5 in 10,000 because they fail to demonstrate the severity of the condition or that the proposed intervention is likely to provide significant benefit. Sometimes the link between the product and the disease is not proven. The likelihood of there being a significant benefit over existing products, or the clinical independence of the proposed indication (i.e. “salami slicing” to reduce prevalence below 5 in 10,000 artificially) are reasons for withdrawal.

Prevalence is sometimes difficult to prove as the data is often lacking. Conditions may also vary in prevalence across the EU, so applicants need to give as full a picture as is reasonably possible in order to satisfy the committee.

To date 60% of designations have been for conditions with a prevalence of less than 1 in 10,000, 30% have been in cases where the prevalence is between 1 and 3 in 10,000, with only 10% in the 3-5/10,000 range.

Significant Benefit

This criteria does not exist in the US orphan drug regulations. It is difficult to define and there are no satisfactory methods to decide if, for example, a proposed new product is likely to provide greater safety or higher patient compliance. Existing authorised treatments are assumed to be “satisfactory” – otherwise they would not have

Where is Research Going?

been given market authorisation so those who would claim significant benefit must show either a clinically relevant improvement or a contribution to patient care.

Other Issues

Availability of existing treatments was not considered unless the restriction on supply is a fundamental consequence of an absolute shortage of the raw material. Nor are claims that biotechnologically produced products are safer than those coming from human or animal sources (the risks may be different, but not necessarily less). Cost is not within the remit of the European Community. Rather it is an issue for member states.

Conclusions

As a result of the regulations being introduced there have been a number of significant benefits for patients with rare disorders. Awareness of the need to develop products has increased, making the process easier and more attractive (for example by increasing recruitment to clinical trials). There is more information available at the European level and patient groups have been able to demonstrate the contribution they can make to successful product development in the field of rare disorders.

Whether this will result in more research remains to be seen, but the signs are good. Once products are developed, questions of availability, pricing and reimbursement and attracting the interest of the medical community remain to be resolved. These are not

What are We Doing About it?

within the remit of EMEA or the COMP and are areas where Patient Groups will need to work alongside other stakeholders in order to ensure that the good intentions that produced the regulations are translated into tangible benefits for patients, with rare disorders.

Workshop I

Access to new treatments – making the system work for patients.

Andrea Rappagliosi. Serono (Workshop leader)

Setting the Scene

Patient access to innovative products is limited and not consistent across the EU. Once market authorisation has been granted there are still significant variations between member states as to when and if the new product will be provided for those who need it by their national health care system.

Market authorisation is a recognition that a product is safe and effective. It could be seen as unethical to deny patients access to such products when they are potentially available on grounds other than clinical ones, that may arise as a result of variation in the nature of disease.

Delays in access can be anything from 2-3 months to several years. In 1999 the average gap between the first member state to agree

Where is Research Going?

reimbursement of a new drug and the last was about two and a half years. This is a reflection of the fact that availability/reimbursement questions are not determined centrally but are decided by member states under the subsidiarity principle.

Limited health care resources means that governments adopt “rationing” techniques to restrict expenditure. However, the process of making an economic evaluation of a medical intervention is a far from exact science. Clearly it is necessary to do so. Resources are not infinite, but there often seems to be a confusion between assessment procedures “does this drug work and for who?” and appraisal procedures “does it deliver what we want?”

Whilst the former is scientific, the latter also brings political issues into the calculation.

The emergence of systems for assessment and appraisal of innovations has potentially introduced delays into the system, retarding patient access to new products and treatments, catching potential beneficiaries between the “rock” of the disease that affects them and the “hard place” of the various forms of Health Technology Assessment being introduced to decide if they are going to get it.

Unfortunately there is a danger of a confrontational approach between industry and regulators denying patient access as the protagonists argue about access, reimbursement and other issues.

Rightly such systems have tended to focus in their early stages on major interventions for common disorders where there is a substantial impact on budgets. Orphan drugs do not fit easily into

What are We Doing About it?

the system developed to tackle these “big issues” as such systems are not easily able to weigh in the balance such factors as:-

- The cost to society compared with the cost to the individual and the family
- The limitations of traditional methods (e.g. clinical trials) of determining effectiveness
- The cost of treatment compared with the real cost of no treatment. Pharmacoeconomics needs a comparator

Delays in the system due to bureaucracy or stakeholder obduracy should be addressed or removed if patients are to benefit quickly. Unfortunately the trend for Finance ministries to secure greater control of healthcare budgets in the EU means that decisions about cost/effectiveness may be taken by those counting the money, not managing the system. This means they may not appreciate the reality of the clinical situation when making resource allocation decisions.

All the “blame” does not fall to public sector agencies, industry too will want to negotiate different prices in different member states. Yet companies know their costs before market authorisation is granted, so it ought to be possible to start price negotiation earlier in the process of getting a drug on to the market. In the case of orphan products, 80% are produced by small companies, which may lack the experience, sophistication and resources to their product bring on to the market simultaneously across the EU, indicating a need for support mechanisms to be developed and provided if patients are to benefit.

Public budgets often seem to be confined to “silos” where saving in one area, resulting from expenditure elsewhere, cannot easily be

Where is Research Going?

factored into resource and cost/benefit calculations. This needs to be addressed. Perhaps there is a case for public/private risk sharing agreement to be developed in order to ensure speedy access for patients.

Discussion

In the Netherlands temporary provisions for making new drugs available to patients have been instigated to overcome delays in the tail end of the drug development process. These might be adopted more widely to the benefit of patients in other member states (with amendment as appropriate) to reflect the organisation of the different health care systems.

Future progress in developing treatments for rare disorders is dependent on research. To ensure that sufficient research is undertaken there is a case for earmarked budgets. Rare disorders individually affect only a small number of people, but because there are so many of them their cumulative effect is large. Such earmarked research budgets would be recognition of the real size of the problem!

Current levels of health care spending are inadequate and should be increased. This is not simply a call for more money to be supplied to industry via national drug budgets unless there can be a clear demonstration of health gain and patient benefit. Money provides the absolute bottom line, but calculation of expenditure will require creativity if a true picture of costs and benefits is to emerge. It is impossible to put a cost on the impact of a condition on a patient

What are We Doing About it?

and their family using current methods. New methods, actively involving patient groups, will need to be developed if health care systems are to be able to evaluate the impact of innovations in health care properly, fairly and promptly. This will result in a broadening of current definitions of cost effectiveness to include indirect as well as direct effects of disease. The current system is too static and rigid. Greater flexibility needs to be factored in if a fair result is to be had.

Innovative treatments are often initially expensive, but as the potential of the technology is realised, so the cost/patient will come down, making it more affordable. In such a situation, if the barrier to access is initially made too difficult this will act as a disincentive to investment, with the result that not only those who stand to gain from the initial development are denied access, so too are those who might have been able to receive treatments as a result of the extension of technology into new diseases.

Workshop 2

Equity of Access to Genetic Services in Minority Ethnic Groups

Aamra Darr: The Open University (Workshop Leader)

Setting the Scene

Patient support groups often do not reach members of minority communities with the condition they wish to address. The same

Where is Research Going?

thing is also found in national health care systems, resulting in a degree of unfairness and inequity, which ought to be unacceptable in a multi-ethnic society. Even in supposedly homogenous societies there is in fact a huge amount of diversity reflecting history, migration and other factors extending back many years. Despite this diversity, there has been comparatively little research investigating the experiences of minority groups seeking to access the health care system.

In the field of genetic services, assumptions about the attitudes of particular groups have been used as an explanation for the failure of the health care system to provide reasonable and fair access. In many cases the assumptions were false, creating a situation where ignorance has fed prejudice, when in fact examination of the actual experience of families would lead to conclusions that would be the exact opposite of the assumption. For example, in the case of UK Muslims of Pakistani origin an assumed lack of take up of services was found by research to result from a lack of information about service availability, not (as had been assumed) fatalism resulting from religious belief. Similarly, no knowledge of pre-natal diagnosis prevented use of this service – once this was provided in an accessible format, families at risk were able to act on it. Education enabled people to act appropriately given the particular specifics of their situation.

Poor communication (either because of language difficulties or inappropriate assumptions being made) results in people stopping going to the doctor thereby reducing the quality of healthcare provided to potentially vulnerable families.

To address the problem it is necessary first to change perception and as a result, change the system if better outcomes for minorities are desired.

What are We Doing About it?

In the context of genetic services this could be brought about by:-

- Providing counselling in people's homes not health centres
- Providing own language counselling
- Promoting the emergence of self help and support groups
- Generating mechanisms for earlier intervention

This would lead to improved clinical care and possibly a lower birth incidence of genetic disorders as families made informed choices.

There is "no one size fits all" model. Populations are not the same, but all decisions are based on information available when a choice needs to be made. Information needs to be interpreted in the light of cultural understanding and beliefs. Kinship networks provide an important channel for communicating amongst affected families. What we talk about affects what we think and the use of language colours the ideas we share.

European society is a multi ethnic one. This is not going to go away and services providers and support groups will need to address the issues that this raises now and in the future.

To be successful minority communities will need to be involved in a bottom up process which embeds the reinterpretation of concepts in all who need to use them. For example, consanguinity is often seen as a "problem" but this is based on stereotypes and an assertion of power by powerful sections of society over the disempowered, resulting in an ideological bias that stops access to services.

Where is Research Going?**Discussion**

The extent to which the changing nature of Europe's population has been recognised is debatable. Does the greater inter-connectedness of the majority lead to isolation, rather than the integration into society of those from minorities? If equity and equality was a reality rather than a goal then the issue would go away, but we have not reached that point yet so we need to have mechanisms that will increase levels of engagement. A "bolt on" solution will not work – instead we must recognise the inclusive multi-ethnic nature of European Society and respond to its diversity rather than criticising its differences. However we must also be mindful of the real pressures on service providers and not alienate them by making demands which they will find it impossible to meet.

In isolated populations the prevalence of specific genetic disorders can differ significantly from the norm for the wider population. This has happened for centuries in many parts of Europe (for example isolated Mediterranean or Romany communities and Jewish groups where marriage outside the group was uncommon). In the UK the most common group where this was observed was in Pakistanis, with the consequence being that the culture was blamed for the perceived "problem".

In Belgium, disempowered groups tended to end up in less well-equipped hospitals, with worse health outcomes. To change this, there must be political will and also public recognition of the fact that access to good quality health care is not the "gift" of the majority to the minority but a reflection of a just and equitable society.

What are We Doing About it?

Practical guides are also needed to facilitate access to services. These should be in the service users' own language and available in a variety of media – print, cassette and video, to allow the information to be re-visited and shared with other family members.

The service providers' own attitudes and values also affect the shape of the service provided. For example, in parts of Europe interpretation is often provided by priests or nuns – people who have a strong set of ethical and moral values and who are often outside official systems for governance, training and monitoring of performance. Whilst many try to be impartial, the particular requirements of genetic counselling and the nature of the possible options to be discussed may act as a barrier to participation by people whose own ethical code may create discomfort or distortion in the process.

Better Advocacy for Patient Organisations in EU Political Arenas.

Ysbrand Poortman and Cees Smit EPPOSI

Introduction

While there has been rapid progress in the treatment of rare disorders in some areas (haemophilia for example is now treatable, but even so it is still a significant pressure on the daily life of those affected) it is still the exception rather than the rule that significant improvement for those with rare disorders will be possible.

Where is Research Going?

In the last decade the number of new interventions made possible by biotechnology has increased substantially and active consideration is being given to a number of measures including:-

- Predictive screening
- Re-combinant DNA derived medicines
- Gene therapy
- Transgenic animals
- Xenotransplantation
- Community genetics
- “orphan” or rare diseases

Despite the potential for good that these hold they are not universally welcomed. Many tend rather to focus on possible adverse consequences. For example, some members of the deaf community see development in genetics as a threat to their future existence if the numbers to be born with congenital hearing loss were to decline sharply. Environmental groups and the “anti-corporate” lobby also express concerns about genetics, although it is not always clear whether these are focused on the science itself or the issue of who is to control its application.

The need for Patient Group Advocacy

In order to make the case for modern genetics and biotechnology patient groups will need to work together, harmonise their activities across the sector and identify common goals and targets if their ability to influence policy and inform the developments and application of new knowledge is to be felt.

What are We Doing About it?

Unless patient groups can organise this then the major global policy and regulatory bodies (such as WHO, UNESCO, WTO, World Bank etc) will formulate their plans and actions without the benefit of patient group input. Patient groups will need to form alliances with other stakeholders across the board (in the public, private and voluntary sectors and at the local, national and international level) if they are to be heard and recognised. Achieving this critical mass will require time, money and energy, but it will also create the opportunity whereby these can be created – perhaps by influencing the funding streams in ways which will recognise the legitimacy and the importance of responding to the (entirely reasonable) demands of those who look to scientific research in the areas of genetics and biotechnology to provide relief from life threatening and debilitating diseases.

The 6th Framework Programme – Guidance on the Preparation of Expressions of Interest

Elmer Nimmesgern. DG Research, European Commission

This presentation gave detailed advice to those considering preparing Expressions of Interest (EoI) preparatory to submitting funding applications under the forthcoming 6th Framework Programme. It was an excellent presentation and gave much detailed and valuable guidelines to those present. It was focused on a deadline, which has now passed, and as such there is little value in reflecting what is now out of date information here.

Where is Research Going?

“Gen-Ed”

Professor Rodney Harris, University of Manchester and Professor Irma Nippert, University of Munster.

Introduction

The scarcity of qualified genetics professionals in the EU means that the quality of services provided is diluted (potentially) by the number of people who need access to them. There is a real difficulty for family care practitioners operating in community settings in recognising genetic problems, and in developing the appropriate skills and knowledge to provide the services that patients need.

The Gen Ed project

This is an accompanying measure for FP5. It aims to establish what is available for the continued professional development of primary care professionals in the field of genetic education. It will also carry out consultations to determine attitudes to genetics and the skills available and which are felt to be needed.

Participating centres are Netherlands, Germany, France, Sweden and Eastern Europe. This cross-community participation will ensure adequate recognition of the diversity of European health care systems. Whilst there are examples of good practice in securing the uptake of genetic information in primary care, this is not generally the case. Very little is in the published literature of how this is being achieved.

What are We Doing About it?

Gen Ed will maintain close collaboration with the US National Coalition for Health Providers Education in Genetics (NCHPEG) project which has had a significant impact on the attitudes of non-doctors to genetic developments.

The outcomes of Gen Ed will be:–

- the identification of core competencies in genetics
- the development of educational materials
- a catalogue of on-line educational materials
- Europe-wide collaborations for professional education and development in genetics for non geneticists
- Europe wide collaboration with patient groups
- National and international meetings to stimulate debate and development in this area

Participation by Patient Organisations in Gen-Ed.

Patient organisations will write proposals for the development of training materials in partnership with academia and clinical colleagues, recognising the fact that virtually all diseases have a genetic component – thereby widening the scope of genetics to make in its impact on the practice of medicine (NCHPEG has the Genetic Alliance, the US patient umbrella group, as a board member).

In Europe, the challenge facing organisations is to change clinical practice in ways that integrate new knowledge and modify services in the light of development. The pace of change, especially in

Where is Research Going?

understanding of common disorders, is accelerating with the possibility of genotype-based treatment programmes being the hallmark of quality services in the not too distant future.

If developments are to be integrated into medical care then family doctors and other community based practitioners will have to understand what such things actually mean, as poor information will result in the wrong interpretation of test results, with bad advice and treatments for patients as direct consequences.

Patient organisations need to address the lack of understanding of the wider familial consequences of genetic information. To do this, a set of core competences defining quality in primary care based genetics must be established. These will need to reflect and respect the perspective of patients and families if they are to be adopted in primary care, because they will only be seen as useful if they do.

Conclusions

A multi-disciplinary approach to delivering genetic medicine will be essential in future if the potential value of our new genetic knowledge is to be realised. At present there is very little integration of services, with the resulting lack of co-ordination resulting in contradictory and incomplete advice being given to patients. This situation is to be found across the EU and in order to rectify it, common issues will need to be defined and specifically national matters addressed.

Patient groups will have a key role to play in ensuring that the outcome of this work reflects their needs and expectations and so helping to ensure that they will be taken up and put into practice.

What are We Doing About it?

DNA Diagnostics – A joint EAGS/EDMA Workshop

What do clinicians need from a diagnostic laboratory?

Prof Domenico Coviello, Clinical Geneticist, Milan

Introduction

Diagnostic information, however it is obtained, is essential in assisting the doctor and the patient to reach an understanding of the situation in which they are placed and how to evaluate the options that may arise as a result. It crosses the boundary between the laboratory and the clinic, but wherever it originates from it will require interpretation if it is to be useful for those to whom it relates.

Before a test is needed

In planning how to deliver a high quality clinical genetics service the clinical geneticist must appreciate what tests are actually available to be called upon, what is their scope (e.g. how many mutations are covered) and their technical limitations and possibilities.

He or she must also know what is available elsewhere and how to access these resources and what procedures are in place for sending and receiving samples. Good communication between clinicians and laboratory colleagues will help to ensure accurate transmission of information in real time, with speedy updates in the light of new knowledge becoming available.

Where is Research Going?

Such direct contact does not always exist. This, coupled with the fact that pressure on resources means that patients are not always seen by clinical geneticists means that there can be problems in ensuring that there is the possibility of explaining to patients what test results actually mean (particularly with respect to their technical quality and coverage).

This difficulty can be compounded by the relative scarcity of skilled genetic counselling support in many parts of the EU, making the patient's decision about whether or not to have a test sometimes more problematic than it needs to be.

When a test is needed

Making the delivery of a service to patients straightforward requires easy access to the system for the patient. Clinicians need to be able to provide information about how to access the system, what the scope and limitations of the service on offer are and what to expect when they get there.

The elements of the services – counselling, testing and medical care – need to be integrated, so the needs of patients can be anticipated and systems set up to meet these anticipations both in the clinic and in the laboratory.

The physical environment must also be right – a single, simple point of access will be crucial, as will systems that ensures the collection and shipping of samples, proper record keeping and holding of information on the technical aspects of handling samples. Also important will be the creation of a proper clinical

What are We Doing About it?

picture that will aid in the interpretation and communication of test results to the patient.

Patient expectations must also be managed. Whereas many medical tests take only a few days, genetic test results, especially when the suspected condition is rare, can often take a lot longer. The way in which the result will be communicated must be clear and agreed by all parties.

For the clinicians to have confidence in the information given by tests, quality standards must be clear and laid down. Biological variability can be accommodated, but errors due to poor procedures are unacceptable.

Particularly important for non-specialists is the way in which the laboratory report is written. Care must be taken to ensure clarity of expression if ease of communication is to be ensured. Standardisation of contact may help in this respect, providing that it allows sufficient freedom of expression and does not become a straightjacket if the patient is to gain a proper understanding of the result. The laboratory must help the clinician by giving clear indications as to the significance of the result.

After the test

Once results have been given patients may need psychological support especially when the result provides a pre-symptomatic indications of a future health problem, rather than a diagnosis of a current one. Other family members may also need support if the

Where is Research Going?

results have consequences for themselves, or for children not yet born – especially when the nature of the condition indicated is not familiar to them.

For possibly involved family members, preferential access to services will be needed. Other involved professionals (non-geneticist doctors) will also need education and advice as to the implications of the finding if the service provided to families is to be logically coherent and thus facilitate high quality care. This is also important if inappropriate investigations are to be avoided, or conflicting advice not given.

Conclusion

Genetic testing is special, particularly when the disease is a highly penetrant, monogenic one, because of the implications of the result for the family. In most other forms of test the relationship of the clinician and the patient is one to one, with the consequence that other specialists may not be alive to the broader familial implications of a result.

To sustain the quality and comprehensiveness of genetic testing services, they must be embedded in a clinical system in which close attention to the minutiae of communication has been given if patients are to get access to accurate, timely and user friendly information.

What are We Doing About it?

DNA Based Diagnostics: Issues in monogenic and common complex diseases and pharmacogenetic.

Prof Klaus Lindpainter, Head of Roche Genetics, F Hofmann-La Roche Ltd, Switzerland

Introduction

Unwrapping the genetic component of common disorder can be seen as a new frontier in medicine. Whilst we can see it approaching and can be reasonably sure what it will look like when we get there, it is not yet with us. This gives us the chance to prepare for it. In so doing we need to examine the extent to which genetic testing differs from other forms of medical test (if at all) and to consider issues raised by the management of common complex disorders such as the possible conflicts between confidentiality and utility or accessibility and quality control.

The Mendelian Paradigm

Mendelian disorders approach a 100% correlation between fully penetrant mutations and their phenotypic manifestation. This linkage also creates the potential for stigmatisation and discrimination, given the widespread public perception of the predictive and inexorable nature of genetics.

Common disorders follow a different pathway, where the mutation leads to an intermediate phenotype, which may result in a health outcome, but this is not necessarily a causal link. Other factors can impact on this outcome. In monogenic disorders the opportunity

Where is Research Going?

to intervene and alter the outcome is small, given current knowledge. In common complex disorders, there is substantial potential for intervention.

Inheritance issues

Unlike the Mendelian disorders, a single SNP (single nucleotide polymorphism) will normally have a small impact on the emergence of the disease. There is a need to look at the whole picture, with all the variables (gene: gene and gene: environment) taken into account. Results of this will be probabilistic, not deterministic. One consequence of this is that there is less opportunity for stigmatisation of those affected – each component will only play a small part in whether or not the disease occurs and this outcome in itself is likely to be more amenable to alterations by preventative or therapeutic measures.

Genetic and Medical Data. Is there a difference?

Once the Mendelian disorders have been selected, the question is whether or not DNA derived information is different from other forms of medical information (both genetic and environmental). Drawing a distinction between the two can be seen as artificial. Pharmacogenomic data is in many ways indistinguishable from other types of medical information except in the public perceptions, which tends to assume that all genetic data is Mendelian in its impact.

This has implications for the introduction of pharmacogenetic information into clinical practice. Defining genetic information as

What are We Doing About it?

“that which is revealed by a DNA test” is too narrow, whilst allowing “DNA and its products” to define genetic information is too wide. It includes almost everything on a medical record, potentially! Equally “monogenic” disorders as a characteriser of genetic information is too narrow and “polygenic” without qualifiers is too wide.

Problems

One consequence of our inability to define genetic information satisfactorily is the creation of regulatory frameworks which are contradictory.

The American SACGT provides an example of this in that it variously defines genetic information as:-

- A. Chromosomes, genes and gene products which are causing or will cause certain diseases and conditions.
- B. Heritable or acquired elements which cause or are likely to cause disease or conditions.

To achieve a satisfactory outcome any definition should identify the root cause of concern. It should recognise the potential for abuse/misuse if any, and of the sensitivity and specificity of any results revealed. The procedure for acquiring it is also important (e.g. the likelihood of false negative or false positive results and what the impact of this might be for the patient), together with both positive and negative predictive value of the information obtained.

In the future it will important to avoid “genetic exceptionalism” – treating genetic data as special per se - but at the same time allowing more respect for the confidentiality of medical information about individuals in general.

Where is Research Going?

Pharmacogenetics

Pharmacogenetics is the mechanism whereby differential drug responses can be established between individuals. It is likely that the use of individual genetic data will allow clinical trial subjects to be grouped according to their likely responses to a particular drug. For this to be acceptable, the FDA (the US regulatory agency) requires a 35% difference in response at present. However the issue is not a black and white one. There is likely to be a difference in degree, not an on/off switch, so interpretation and generalisation of results will require caution in practice.

The pharmacogenetic scenario is related to the specifics of disease pathology. Patient stratification in drug development will be in the context of specific DNA markers as predictors of likely response. This potentially raises ethical questions about the acceptability of defining populations and developing treatments for specified subsets. Communicating how the underlying biology affects the outcome will need explanation and education (both sadly neglected) if it is to secure public support, rather than fuelling people's fears about genetics. Unlike other forms of medical information, which people often seem remarkably casual about, genetic (or perceived to be genetic) data seems to create high levels of anxiety. If, as a result, regulation focuses too heavily on data protection and privacy issues, then the result is likely to be limiting on the utility of the information and reduce patient benefits as a consequence.

Conclusion

We need to develop a societally-endorsed consensus about the uses to which genetic information (appropriately defined) can be put for

What are We Doing About it?

patient and public health. This will be accompanied by dialogue with the public, probably coupled with a realisation of the need to safeguard all forms of personal medical information better.

Providing a service, an industry perspective.

Dr Erik Tambuyzer, Vice-President, Corporate Affairs Europe, Genzyme Corporation, Belgium

Introduction

According to an OECD study in May 2002, patient samples for molecular genetic testing purposes are crossing national boundaries with increasing frequency. This happens in the EU as well as elsewhere in the world and for European citizens it raises issues to do with the giving of informed consent, the quality assurance procedures in place for allowing results to be properly interpreted and also that of laboratory accreditation.

An Industry Perspective

Much of the interest in DNA diagnostics has arisen as a result of developments in biotechnology. 25% of new therapies are now biotechnology based and 82% of clinical trials require a biotechnology result of some kind – for confirmation of diagnosis for the delivery of treatment or some other purpose.

Increasingly, serious and chronic disorders are being treated, with a correct and precise diagnosis being essential for appropriate therapeutic delivery to be organised. In this context, the relatively

Where is Research Going?

poor characterisation of many rare disorders may become an important limiting factor in the development of new therapies.

Genetic Testing

Since the 1960's commercial laboratories have provided chromosomal analysis. In the 1990's molecular testing also became available. As knowledge advances, testing becomes more complex creating cost pressures and delivering new possibilities at the same time.

Issues

Increasing costs result not only from increasing technological possibilities, but also from increasing regulatory controls. The expectation that industry-provided services will have appropriate quality assurance and quality control standards in place provides a competitive spur to academics and public sector service providers.

Economies of scale will allow a trade-off between price and quality, but this may come at the expense of tests for very rare disorders, for which services may remain in public sector laboratories.

Population screening, if it becomes widespread, will also create pressures for commercial involvement either through service provision on a contract basis or by the development of test kits for use elsewhere.

An increasing awareness of liability as an issue is a major driver for increased quality standards in both the public and the private sector. In the field of cytogenetics, for example:-

What are We Doing About it?

- There are no uniform standard for quality across the EU
- Many small laboratories are providing a limited range of testing
- There is a need for an accepted accreditation system to drive standards up.

In the molecular testing arena, commercial sector involvement has allowed input to the development of standard operating procedures for routine tests and the scaling up of service delivery with a potential increase in quality and consistency of results. The increasing specificity and sensitivity of testing is creating new paradigms for testing. In order to have clinical validity, the outputs of testing laboratories must be rock solid and dependable.

Ethical and societal issues

The emphasis in all service-providing laboratories should be on constant upgrading in quality control and quality assurance in order to ensure the timely supply of reliable information to physicians and patients. There is also a responsibility to contribute to public understanding about the limits and possibilities of genetic testing in a reliable and measured way if expectations and/or anxieties are not to be unnecessarily inflated. From an industry perspective the key drivers of a genetic testing service are:-

- The quality of the result
- The availability of the result

Technology and methodology are not in themselves important except insofar as they contribute to the above. New developments in the pipeline such as pharmacogenomics will only act as further drivers towards increase high quality service provision.

Where is Research Going?

Conclusion

Knowledge is increasing almost on a daily basis. In order to ensure the appropriate use of this new knowledge a degree of regulation and harmonisation across the EU will be needed. This can best be achieved through a partnership between industry, patients, academics and clinicians in the development of a common framework for meeting patient need wherever the service is provided.

Measuring and maintaining quality in DNA diagnostic laboratories.

Dr Rob Elles, Head of DNA laboratory, St Mary's Hospital, Manchester

Introduction

For the scientist, accuracy is probably the starting point as a definer of quality, whilst for the patient the first question is probably one to do with getting access to a service in the first place. Access is made up of a number of dimensions, including: -

- Geographical proximity
- Cultural barriers
- Financial availability
- Timelines – including the research into service gaps and the access to the latest technology
- Accuracy of result

What are We Doing About it?

- The communication of the result to the clinicians (with understanding and interpretation acting as measurable parameters of this)

Process

A genetic test starts with contact between a patient and a clinician with a decision being made that the resolution of the presenting problem requires that tests are carried out in order to make relevant information available.

The laboratory does the tests, but its responsibility does not end with the completion of the technical process involved. The laboratory should also provide fully interpreted reports to facilitate the genetic counselling process – remembering that in many cases the test results do not go to the clinical geneticists but to colleagues in the other medical specialisms such as paediatrics or neurology.

In order to develop and maintain standards in professional practice many genetics labs participate in a process of external quality assessment (EQA)

EQA

The EQA system uses test cases to mimic the path of a sample from the initial contact with the patient through the lab and of the results back via the clinician to the patient. The system looks at issues such as the preservation of patient data as well as the technical adequacy of the procedures adopted.

Where is Research Going?

The expectation that laboratories will participate in EQA on a year-on-year basis is not a familiar one and for many this is a culture that still needs to develop, but the benefits for quality of service for patients can be reflected in declining error rates over time (in one disease specific UK National External Quality Assessment scheme, around 35 laboratories from the UK, Ireland and the Netherlands that have participated regularly have recorded no genotyping errors in the last 5 years).

The system in place is able to differentiate between sample and data handling errors and has developed criteria for good practice in reporting results. These include: -

- Correct identification
- A re-statement of the reasons for referral
- The methodology used to obtain the result
- The actual results (raw data)
- The conclusions to be drawn from those results
- Any further work required
- Implications for counselling
- The authorisation of the report by a relevant senior staff member

Accreditation to externally monitored standards is the guarantor of quality for service users – especially for patients, whose information needs to be at the centre of many diagnostic services.

What are We Doing About it?

Conclusion

Recognition of the importance of a patient-centred approach linked with the adoption of relevant quality standards (such as ISO 17025) leads inevitably to a process of continuous audit of quality and results in pressure to develop and improve standards. For patients this provides an optimistic picture for the future, with increasing availability of a widening range of tests, accurately carried out and appropriately and sensitively communicated, facilitating choice, giving control and achieving autonomy in difficult situations.

The need for fast and accurate diagnosis – the patient perspective.

Ysbrand Poortman, (Formerly Executive Director) VSOP, Netherlands

Introduction

Genetic diseases historically have been seen as incurable and untreatable. For some this has been taken as a disincentive to work towards a diagnosis – reflecting perhaps an out-dated attitude that “bad news always comes too early”, or perhaps a reluctance to be the one who has to impart this to a patient or their family.

Patients, however, want and need this information in order to understand what has happened to them. A delayed diagnosis means that potentially avoidable consequences may not be avoided. It also has potential implications for the ongoing care of the affected individual, in that, without a diagnosis any possible treatment

Where is Research Going?

cannot be provided. There are also possible knock-on effects for the wider family and the reproductive choices that those potentially at risk may wish to make.

Genetic disease affects all sectors of society. It spans generations and involves the whole family in ways that other types of ill health often do not.

What do families want?

In essence families are looking for:-

- Relevant information
- More and wider information
- Access to specialist help
- Information about the probable progress of their disease
- Access to early detection and accurate diagnosis (linked to the best available care and treatment)

Provision of this has implications for the shape of future EU health care systems. Properly organised, relevant information (as defined above) helps to:-

- Eliminate or at least reduce anxiety and uncertainty
- Prevent “shopping” for treatments that will not work and which may do harm
- Prevent repetition of the event in the same family
- Protect family relationships by reducing blame and recrimination
- Permit lifestyle choices

What are We Doing About it?

Access to testing

Testing is relevant for families, but they can sometimes be denied access because there is little apparent medical or economic benefit to be had. Yet it is impossible to put a cash value on the benefit of information to an individual or family. If the test is available and people make a considered choice about whether or not to be tested, then society ought to support the access to the information that the test will reveal. However, the autonomy of the individual should not be infringed, either with regard to whether or not to be tested or the uses that the resulting information may be put to.

Possession of information allows new options to be developed – including the ability, for example, to recognise a predisposition and instigate early interventions on the onset of symptoms or develop other types of improved health care for the individual or the family.

The role of patient groups

Development of adequate and equitable diagnostic services requires patient groups to work together in developing and providing information, in campaigning for increased flexibility in health care systems and in pressing for developments which will both incorporate new knowledge quickly and effectively and make best use of available resources. For example, the creation of a pan-European network for providing diagnostic tests for very rare disorders ought to be a goal which patient groups could work together to achieve.

Where is Research Going?

Patient groups need to work with service planners to ensure that new knowledge is incorporated into services in ways that reflect patients' needs. This may include shifting resources from the management of existing disease to their prevention by the introduction of health maintenance measures, including lifestyle changes, targeted treatments (including providing these pre-symptomatically) and other interventions to raise awareness and provide choice.

Conclusions

Without proper attention to early and accurate diagnosis, patients will be denied the opportunity to understand their situation and make choices about future options. Lack of diagnosis also prevents systematic planning for the assimilation of new knowledge into health care systems and the development of strategies for the reduction or prevention of the burden of disease on families and on society as a whole.

Concluding remarks

John Place, Executive Director, EDMA, Belgium

The development of an increasing range of genetic tests capable of providing a widening range of diagnostic information will have implications for health care systems. More particularly it will have consequences for patients and their families.

The realisation that an increasing number of common conditions have a high heritable component will change the way we think about disease risks. This coupled with developments in

What are We Doing About it?

pharmacogenomics, will also change the nature of the responses we are able to make to these.

Genetic information will need to be integrated with other factors such as the range of possible variations in therapeutic outcomes if an economic case for treatment is to be made. (In the US the high cost of certain drug treatments means that genetic tests to identify likely beneficial responders are becoming a requirement prior to permitting reimbursement). The EU is unlikely to be far behind in developing methods for selecting patients suitable for treatments with new drugs.

The information revealed by diagnostic tests is likely to prove more important than the technology used to reveal it and the strategies developed for dealing with that information will be critical in determining its societal acceptability and hence the potential for patients to benefit.

Issues such as:-

- Confidentiality (especially given the fact that the health system is often not very secure)
- Rules for dealing with questions arising from more medical uses of genetic information in contexts such as insurance or employment.
- The right to know and the right not to know
- The familial implication and the consequences for other family members of my decision to find out (or not to find out) about my "genetic status"

Where is Research Going?

Genes are a family concern. To enable families to make use of the information potentially revealed by exploration of their genes there needs to be:-

- The opportunity for early accurate diagnosis
- Access to objective accessible information
- Appropriate guidance for individuals who are tested
- Access to effective treatments where these exist
- New clinical resources to enable the application of genomics to medicine (in regard to genetic data with clinical effectiveness)

To achieve this, we must address the issues created by our failure to make this happen in any meaningful way for many European citizens. The lack of understanding amongst physicians, poor communication, limited access to information, the lack of funding and a general tendency to medicalize health issues are all barriers which need to be overcome. To do this will require a significant injection of new resources and improved access to testing, coupled with a systematic programme of public and professional education. Most of all it will need professionals, politicians and planners to listen to patients and their families. They must respond to the consumer's legitimate expectations for information and knowledge. Accessibility to objective information will enable health care systems to provide the necessary support for better decisions in health care appropriate to the needs of individuals and their families.

What are We Doing About it?

Appendix One

Statement of the Parent and Patient Organisations (EAGS)

The Necessity of Early Detection and Accurate Diagnosis

Early detection and accurate diagnosis of diseases accompanied by information individually/group tailored, well balanced and timely, comprehensive, reliable and up-to-date, with appropriate guidance, and of course preferably followed by effective treatment, is a high and increasing priority for, us as patient organisations but also for Europe.

The European health system of tomorrow will have to satisfy the growing needs of the concerned individual, to learn early, well document, his risks and his options regarding prevention and therapy.

I. The Promise of In Vitro Testing

Information about the body can be obtained in a number of ways: by imaging and scanning to get morphological and functional information, by physical measurements of temperature and weight etc., by electro-medical measurements such as ECG or EEG and by the measurement of biochemical and genetic parameters using in vitro tests.

There is a need for more effective use of in vitro testing to provide early and correct diagnosis as the foundation for effective treatment: early diagnosis because it is in the interest of the individual concerned to detect disease at an early stage when chances of cure are highest, and correct diagnosis because a wrong diagnosis

Where is Research Going?

inevitably means ineffective treatment, and no diagnosis often means no treatment. Early diagnosis can also be of interest for primary or secondary prevention by family planning and lifestyle issues.

However, in vitro tests are not just used for diagnosis. They also provide objective information that forms the basis for better medical decision-making. It is this informational aspect that differentiates in vitro tests from other medical devices that are used to treat patients. It is no longer sufficient to give treatment without closely monitoring the result in the individual treated. In vitro diagnostic testing has an important and increasing role to play in monitoring the treatment given to individuals to determine if it is having the desired effect – this is called “theranostics”.

Early testing and accurate diagnosis can make a vast contribution towards a new paradigm of health maintenance beside the old paradigm of disease management.

2. The Reality of Diagnosis

Individuals and their families who are affected by genetic, multi-factoral and/or chronic disease have often experienced late and often vague diagnosis. In their experience, many physicians do not understand or utilise the breadth of laboratory testing options that are now available. In 1998, a survey of knowledge about in vitro testing undertaken by Watson Biomedical in the United Kingdom showed that physicians have a general lack of awareness of in vitro tests.

What are We Doing About it?

Individuals have often experienced that not only is information about the tests and the diagnosis limited, it is poorly communicated, and that support for the implications of the diagnosis and for coping with the disease is scarce and difficult to find. Rather than just providing data, more information needs to be made available to healthcare providers to allow for easier interpretation of results.

Physicians also are not always aware of what it means to live with the reality of an undiagnosed or untreated disease, while individuals, on the other hand, are often unaware of the advantages of knowing their diagnosis and how to use this information to plan or even to improve their future quality of life.

Finding out whether someone is at risk for a particular genetic condition can be important to help them plan preventive measures or help them to make better decisions about their future. The following examples illustrate the necessity for early and accurate diagnosis of illness and disease.

- (a) There are reports of families with three or more children suffering from the same deteriorating disease, born one after another. These parents were not warned about pre-conceptual screening or given genetic counselling early enough after the birth of their first child, and because Duchenne’s muscular dystrophy manifests itself around the third or fourth year of life these parents had further affected children. This X-linked muscle wasting disease can be detected by a simple CK bloodspot test at birth.
- (b) A father signs a contract for a job hundreds of kilometres

Where is Research Going?

from home and soon after hears that his three year old daughter who has suffered health problems since birth, has finally been diagnosed with a progressive metabolic disease that will require his presence and time at home. The disease could have been detected at birth and the father would not have signed a contract to work so far away.

- (c) A family bought an apartment on the fourth floor in a building without a lift. A short time later, their child developed a progressive paralysing spinal muscular atrophy. If the disease had been detected earlier, the family would have found a more suitable housing arrangement.
- (d) A man, after many years of worrying, applied to a medical help desk, explained his concerns about various members of his family dying at about age forty and inquired about his own risks of early death. Subsequently, he discovered that his family members who had died had suffered from the cardiac problem Familial Hypercholesterolemia (FH). This individual learned about FH, and took the information to his doctor. He underwent genetic testing and was diagnosed with the same problem. He was fortunate to be able to receive treatment.

3. Advantages of Early and Accurate Diagnosis

Accurate diagnosis eliminates uncertainty, reduces anxiety, and prevents the costly, frustrating and time-consuming odyssey of shopping through different healthcare systems. It allows for early treatment and management of the condition. In the case of a child born with a genetic disease it offers the possibility of avoiding

What are We Doing About it?

repetition within the same family, protects the relationship between the parents, provides options for future family planning and enables the family to make appropriate life style choices.

As already stated, treatment is only one of many reasons for early and accurate diagnosis. Screening and testing for, as yet, incurable or untreatable diseases can be very relevant for families. People should not be denied access to tests merely because there is no medical or economic benefit, and they cannot be reduced to their “treatability” in the health care system. The information that in vitro testing can provide should be supported rather than suppressed. One should first ask if there is a benefit for the individual, look at the clinical and medical benefits, and only then ask the questions: Is it affordable and who should pay?

The question as to whether we can afford certain medical interventions is an important but separate issue from the fact that individuals may want to have certain tests done. They may even be willing to pay out of their pocket for the information that will be provided. From the perspective of an individual and his family, a negative test result and the assurance that nothing is seriously wrong is extremely valuable information that will reduce anxiety and uncertainty about the future. On the other hand, others may find that the reverse is true, and they would rather not know their test results.

Certainly, there is room to challenge the conventional thinking that has led to present attempts to limit individual responsibility for health. Health is a good investment, not just for us all as individuals, but for society as a whole.

Where is Research Going?**4. Requirements of Diagnostic Testing**

Most laboratory tests in Europe are used in the management of disease. Although there are a number of tests that could be performed as part of health management, for example testing blood cholesterol or lipoprotein levels as predictors of heart disease, usually healthy people do not ask for such tests. Factors that play a part in this choice are the inconvenience of going to a medical laboratory or to the doctor's office to have a test performed, and waiting for the result. Laboratory tests today, can be developed in formats that are suitable for public use and give rapid results.

When such self-tests are available, as has happened with pregnancy tests, they tend to be well accepted and widely used. In general, the public understands that tests can be performed incorrectly, that they can require additional testing before the result is certain and that the doctor may need to be consulted. Even tests requiring blood sampling can be developed into user-friendly formats for self-testing. Blood glucose tests for monitoring diabetes is a good example of this.

The following should be taken into account when considering diagnostic tests: –

- Diagnostic self-tests must be designed specifically for the type of person who is using them. For example there may be special language requirements or a need for a large visual display. Because lay people are not expert in using tests they may need extensive training and for this reason it may be more expedient to encourage self ordering of tests rather than self-testing.

What are We Doing About it?

- Any diagnostic test should be accompanied by clear, inclusive and well-balanced information that is specially tailored for the layperson. Preferably, this information should be produced in consultation with relevant professional and patient groups.
- A person taking a test should preferably consult with a family doctor, specialist and/or counsellor. This is advisable but should not be mandatory. Accessibility to testing and information about testing is most important.
- The person tested should have access to trained professionals with appropriate support (e.g. a doctor, a nurse or a counsellor) if results are outside the normal range, so that they can be properly assessed and confirmation tests taken if necessary.
- Some genetic tests may require education and counselling beforehand to ensure that the person being tested understands the test to be done, the potential results of the testing and other issues that may need to be considered. Counselling sessions and/or support must be provided if test results are confirmed to be unfavourable.

Society should in no way contribute to: –

- The infringement on the autonomy of the individual's choice either to use or not to use tests. The individual concerned must decide whether or not testing is appropriate for them and whether or not they want to know the results. There should be no pressure placed on the individual to choose, or not to choose testing. In addition, they must decide who, if anyone should have access to their test results - including the doctor. There must be complete freedom to make these decisions even in the event of conflict without societal repercussions.

Where is Research Going?

- In a case where people with a disease or handicap are considered as “cases of missed prevention”. There may be disadvantages for the individual. For example, a diagnosis may label the individual diagnosed as a “medical case” and societal pressure may decrease personal freedom of action and choice. Rather than choosing to have a therapeutic abortion for a pregnancy affected by Down’s syndrome, a family may decide instead, to carry on with the pregnancy, have the baby and care for the affected child.
- The stigmatisation and discrimination because of the decision to have diagnostic testing (including genetic tests to determine future risks) or because of the decision to decline testing. This specifically refers to banks, employers and insurance companies.

5. The Future of Diagnostics

In vitro diagnostic testing presents exciting opportunities for the future.

Diagnostic testing is already highly technological and well developed and the reality of the recent advances in this arena are truly phenomenal. The Human Genome Project is forging ahead and with the identification of new markers, the genetic background for common disorders and rare diseases is being unravelled and molecular biology is facing new dimensions. This is relevant for rare diseases and common diseases such as diabetes, various cancers, Alzheimer’s disease, and different forms of heart disease.

Thanks to the rapid advancements at the bio-molecular and genetic level, the availability of tests for early, pre-symptomatic detection and screening, for susceptibility and carrier status for disease will continue to increase considerably and a wide range of tests and self-

What are We Doing About it?

tests will become more available. These tests will be welcomed as they enable people to act early according to their own wishes and needs.

New in vitro tests are already opening up a future of individualised medication. These new advances are known as “genomics” or “proteomics” depending on whether they are based on genetic information or knowledge of the proteins involved. New drugs are being developed to suit people who, on the basis of in vitro tests, are shown to be receptive to treatment and will allow selection of individuals that can tolerate powerful drugs that, in other people, give intolerable side effects. The prognosis and monitoring of such treatments is dependent on laboratory information. Perhaps the most well known example is the measurement of the HER-2 receptor to predict whether breast cancer will be responsive to the medication Herceptin.

In addition to the applications for developing genomic pharmaceuticals, information from genetic tests can also be used by individuals to make life style choices (e.g. those affected by Familial Combined Hypercholesterolemia). This is part of the overall trend towards empowerment of individuals, where emphasis is placed on the prevention of disease, on health and on wellness testing.

Information is becoming readily available to consumers as well as health care professionals through the Internet - eHealth. People are beginning to use this information to their advantage because they can obtain comprehensive up-to-date health information and access health care services (information about disease prevention, diagnosis, and treatment options including laboratory testing, self-care, interactive check-ups, etc.). It is reasonable to say that relationships between their doctors will undergo fundamental change. In fact, they may even consult with a physician online before they see their own family doctor.

Where is Research Going?

In contrast to this positive view of the future and increasing demand for in vitro testing is the constant pressure to cut the costs of the public health system. In fact, because the marginal cost of performing in vitro tests can be very low, additional information from IVD tests can be obtained at little extra cost. On the other hand, increasing the amount of diagnostic testing will no doubt have an impact on the demand for health care and will be seen as creating a burden on the health care systems of Europe. This means that, although a diagnosis may be of great value to the individual and his family, it may not be cost-effective for society as a whole.

In order to increase the value of medical interventions and to select interventions with high quality in relation to their cost, health economists and the medical professions increasingly look at the evidence for the effectiveness of medical procedures and practices. Objective information from in vitro testing often provides the evidence that is needed in the growing implementation of this Evidence-Based Medicine (EBM) approach. One element of this approach is to look at new technologies (medical procedures) and assess their utility before they become routinely used. Here again much of the objective data for Health Technology Assessment (HTA) may come from in vitro testing.

6. Recommendations

Because of the ongoing developments of in vitro diagnostic tests, society must be prepared for the new options brought forward by molecular biotechnology and genetic knowledge in order to optimally benefit from them. The application of such tests requires continued surveillance and adjustment to improve the quality of

What are We Doing About it?

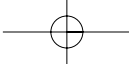
health care delivered to individuals. Attention should be given in future to finding the genetic markers that indicate predisposition to disease, not just for the informational value this has for the individual, but also to be able to select sub-populations for screening and treatment.

Scientists, industries, clinicians and patient organisations must work together to provide and increase the availability of reliable, effective, simple and inexpensive tests. This can be achieved through stimuli and economic incentives for researchers and for in vitro diagnostic test manufacturers, a higher level of awareness of clinicians of available diagnostic tests and clear and realistic expectations from individuals and patient organisations.

This means ongoing education to all individuals, providing flexible healthcare systems in which a knowledgeable public can manage information and use it for their own benefit. Making young people aware of their health status through education and various health promotion activities with respect to the wide range of simple laboratory tests may be an initial step in this complex process.

It may also be necessary to establish a network of laboratories at the European level in order to provide services that are not available at the national level. The cost of testing must be covered by each country's National Insurance or by the hospital.

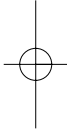
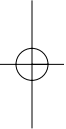
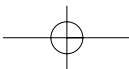
Finally, more study is required about the ethical, medical, social and technical implications of screening.



Where is Research Going?

Notes:

What are We Doing About it?





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