What can be offered to couples at (possibly) increased genetic risk?

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Abstract We review the reasons why a couple might seek specialist genetic counselling about a possible reproductive risk and the options available to them. Most commonly, the couple will be concerned about the risk of recurrence of a medical condition that has already occurred in the family. Sometimes, the increased risk may come from their ethnicity or because of a consanguineous marriage, rather than because any problem has occurred previously. The geneticist must identify the exact nature of any problem and determine the risks in the light of the mode of inheritance, any investigations undertaken and any other relevant information. The geneticist will then review the options open to the couple, and help them arrive at their own decision in a non-directive way. Some couples may opt to do nothing and let nature take its course but others may request prenatal or pre-implantation diagnosis, or they may avoid the conception of an at-risk child by using donor gametes, adoption or even decide not to have children.

Keywords Genetic counselling · Genetic risk · Pre-implantation diagnosis · Prenatal diagnosis

A couple may approach the primary care team seeking preconception or early pregnancy genetic advice for a variety of reasons, including:

- A possibly heritable condition in one (or both) of the couple
- A history of infertility or recurrent pregnancy loss

- A family history of one or more possibly heritable conditions
- The couple is from a population group with a high frequency of certain genetic diseases
- The couple is blood relatives (a consanguineous marriage)
- The couple is anxious about reproductive risks, even though there is no specific indication that they are at increased risk.

The couple may themselves seek genetic advice; alternatively or additionally, a medical professional may suggest they seek advice even if they themselves may not have raised any concern, because the professional is aware of a potential genetic problem in the family. People referred to the genetic clinic by another specialist without much discussion, rather than themselves asking for the referral, may have very little idea why they are there and may never have supposed they had any genetic problem.

An important role of the primary care team is to decide which families require referral to a specialist genetic centre. In many cases, members of the team, depending on their level of knowledge and training and access to appropriate resources, will be able to deal with issues raised. Other cases need specialist advice. If the couple have had a previous child with a genetic problem (or an affected miscarriage or stillbirth), they will most likely need referral to discuss the option of prenatal diagnosis. Similarly, those potential parents who themselves are affected by a monogenic disorder or who have been picked up as carriers on screening are likely to need referral. After a pregnancy has been established, the commonest indication for referral to genetic services is a condition or potential problem detected by foetal imaging or by antenatal screening tests.

Whether in the specialist clinic or in primary care, the intervention goes through two stages: first identify and quantify the risk, and then review options, given the genetic risks. Choice is a major factor in preconception and prenatal

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care and assumptions cannot be made by the professionals about what is the ‘right’ course of action. A couple may have a very different agenda from the one that a doctor or counsellor would suppose, given the family situation.

Identifying the risk

The sections below outline the major common problems. More detailed discussions of modes of inheritance and genetic risks can be found in any of several textbooks, for example Read and Donnai (2011).

A possibly heritable problem in one or both members of the couple

The commonest conditions that prospective parents may want to discuss are those where there may be a familial predisposition but where there is no defined inheritance pattern. These conditions include epilepsy, bipolar disorder, multiple sclerosis, asthma, diabetes, or any one of a host of complex multifactorial conditions. In general, any child of theirs is at increased risk of being affected compared to the background risk, and the risk is further increased if there is a relevant family history on both sides. The magnitude of the risk must be identified through empirical survey data, not by applying any genetic theory, although it must be borne in mind that small subsets of many common conditions can be monogenic, being due to the effects of a single highly penetrant gene. This is particularly important for the common cancers like breast and bowel cancer. For many complex conditions, the incidence varies with both time and place, and the recurrence risk is usually a function of the occurrence in the population. For this reason, it is important to use a survey that has been conducted in the same population as the consultands (taking into account both ethnicity and geographical region), and that is recent in date. As well as considering the recurrence risks of the condition, it is also important to consider the potential teratogenic risks of drugs given to treat the condition in a woman who is pregnant. Women on anticonvulsant medication, in particular, need to have their regime reviewed by their neurologist pre-conceptionally; while for pregnant diabetic women, glucose control is extremely important and should be monitored closely in a specialist obstetric clinic.

In some cases, the problem may be a monogenic condition with a known mode of inheritance. Perhaps one partner has phenylketonuria but is functioning normally, thanks to successful dietary treatment. PKU is an autosomal recessive condition, and while any child will necessarily inherit one copy of the pathogenic mutation from the affected parent, it is not at risk of developing the condition unless the allele it receives from the other parent is also a mutant version. With

a disease frequency of 1:10,000 the carrier frequency is 1:50. In many cases, a DNA test can be used to check whether or not the partner is in fact a carrier. If the patient is a woman, she needs to follow the diet meticulously throughout pregnancy to avoid harmful effects on the foetus, regardless of its genotype.

For many families where an X-linked recessive disorder such as Duchenne muscular dystrophy is segregating, the family knows only too well about their risks, and often females have had their carrier status clarified. However, even in such families, there can be misinterpretation and a preconception visit is an opportunity to check this. Problems arise when a condition *might* be X-linked but where the situation is not clear. This often happens with non-syndromic intellectual disability in a boy. In these situations, a detailed family history is essential, but even after this and laboratory investigations it still may not be possible to give precise estimates of risks.

Different situations arise when the condition is dominant. In the case of achondroplasia, the most common type of dwarfism, the risk for the child of a couple where only one parent is affected is 1 in 2 and an affected child will have similar clinical features to the parent. However, if both the man and the woman have achondroplasia there is a 50 % chance of the child being an affected heterozygote, a 25 % chance that the child has normal stature and a 25 % chance that the child inherits the mutant gene from both parents and has the lethal form of the condition. Other dominant conditions are not so predictable—for example neurofibromatosis or myotonic dystrophy. The risk a child will inherit the pathogenic mutation is still 1 in 2—but it is often much harder to predict how severely affected such a child would be. Many dominant conditions show very variable expressivity. Even people carrying exactly the same mutation at the DNA level may show very different clinical symptoms. Moreover, for an affected person to be in an adult relationship and contemplating having children, they are probably towards the mild end of the spectrum. It may be very difficult for them to fully take on board the risk that a child who inherits the same gene as themselves may be much more seriously affected. Mostly such variation is random, due to unknown genetic modifiers or maybe pure chance, but myotonic dystrophy and related ‘dynamic mutation’ conditions are a special case where the severity increases systematically down the generations.

A history of infertility or recurrent pregnancy loss

A common reason for seeking genetic advice is when the couple has a history of infertility or recurrent miscarriages. Infertility is defined as the failure to conceive after 12 months of unprotected intercourse. There are many genetic causes of infertility, especially in males. Among the

common anatomical and hormonal causes are a number of genetic conditions where specific counselling can be offered. If these have been excluded, chromosome analysis would be a first investigation, using microarrays that can detect small deletions (deletions of part of the Y chromosome cause up to 15 % of male azoospermia) as well as gross numerical abnormalities.

It has been estimated that 10–15 % of all clinically recognised pregnancies end in a miscarriage. Recurrent miscarriage is defined as the loss of three or more pregnancies. There are many possible causes; more than one contributory factor may underlie the recurrent pregnancy losses which affect 1 % of all women. Only a proportion of women presenting with recurrent miscarriage will have a persistent underlying cause for their pregnancy losses. Maternal age and previous number of miscarriages are two independent risk factors for a further miscarriage. All couples with an unexplained history of recurrent miscarriage should have peripheral blood karyotyping performed. In approximately 3–5 % of such couples, one of the partners carries a balanced structural chromosomal anomaly. The most common types of parental chromosomal abnormality are balanced reciprocal or Robertsonian translocations. In a future pregnancy there is a 5–10 % chance of an unbalanced translocation, and prenatal diagnosis can be offered.

A family history of one or more possibly heritable problems

As detailed by Bennett (2012), every genetic consultation should start by taking a detailed family history and drawing up the pedigree. Each partner should be asked systematically about any previous children and about their parents, siblings, uncles and aunts, grandparents and cousins, noting in each case any important medical history and, where appropriate, the age and cause of death. It is important not to ignore one partner, just because the supposed problem lies with the other partner's family. Ethnic origin and place of birth are important in considering risks of recessive conditions.

Family reports may need to be confirmed by checking the relevant medical records. Probands may be able to find more information from their relatives, but such information should be treated with a degree of caution, and relevant medical records may need to be consulted, with appropriate consent. Family beliefs about illnesses and causes of death may be unreliable. People may not know the precise medical details of their relatives' illnesses; they may miss connections or imagine connections that do not exist. A supposed strong family history of breast cancer may, on investigation, turn out to be a mother and great aunt who died of late-onset breast cancer and two other female relatives in a large family who had cancer of the pancreas and of the colon, respectively. Conversely, an uncle who was deaf may have had

type 2 neurofibromatosis with acoustic neuromas, and a child who died of infection may have had an immunodeficiency syndrome.

Information about earlier generations is often inadequate by present-day standards. Moreover, a diagnosis that is adequate for management of a patient may not be sufficiently precise for genetic purposes—for example, it matters precisely what form of muscular dystrophy a deceased relative had, because different forms have different modes of inheritance, even if they required similar management. It may be appropriate to request diagnostic tests, either on a living affected relative or, more probably, on stored pathological specimens or neonatal blood spots from deceased family members.

Depending on the condition, it may be relevant to examine the consultands and/or to perform diagnostic tests.

- For many variable dominant conditions, the geneticist must know what minimal clinical sign may indicate that a consultand in fact carries the family mutation. For type 1 neurofibromatosis, the examination would look for café-au-lait skin patches; for Treacher–Collins syndrome the geneticist would look for a notch in the lower eyelid of an otherwise apparently normal person; for type 1 Waardenburg syndrome the minimal sign would be a wide spacing of the eyes (dystopia canthorum). Such signs would show that the consultand, though perfectly healthy, carries the family mutation and any child is at 50 % risk of inheriting it, with possibly much more serious clinical consequences.
- Carriers of autosomal recessive conditions could be identified by DNA testing, or more rarely by haematological or biochemical tests, for example haemoglobin S for sickle cell disease and hexosaminidase A for Tay–Sachs disease. DNA testing is much simpler and more certain if the family mutation has already been identified in an affected family member.
- Female carriers of X-linked recessive conditions sometimes show patchy or minimal signs of the condition. DNA testing could make a definitive diagnosis.
- Chromosome analysis is appropriate where there is a family history of unexplained miscarriages, stillbirths or babies with multiple congenital abnormalities. For this particular purpose it is better to use traditional karyotyping rather than one of the microarray-based techniques that are now supplanting karyotyping for most applications. The main risk is of balanced structural rearrangements, and these do not show up on microarrays (but can be picked up by paired-end sequencing). If a consultand is identified as carrying a balanced chromosomal abnormality (a translocation or inversion), the risk of producing unbalanced and abnormal offspring depends on the position on the chromosomes of

the breakpoints. Expert cytogenetic advice should be sought.

- If a woman carries a pathogenic variant in her mitochondrial DNA, every child will inherit the variant, but the clinical consequences of having such a variant are notoriously hard to predict. Some of this uncertainty results from the fact that there is often mosaicism (heteroplasmy) for the mutation and the proportions of mitochondria with the mutant and normal versions within and between cells in the child cannot be predicted. On the other hand, if the carrier is male the children are at no risk, because a man does not transmit his mitochondria to his offspring.
- For multifactorial or complex diseases, survey-based empirical risks are given, as explained above. In the past few years, a large number of genetic susceptibility factors for multifactorial conditions have been identified. These are common DNA sequence variants that modify a person's risk of developing one or another disease. However, their effects are very weak and they do not provide useful predictions of individual risk, even in combination. Genotyping for them is not warranted.

As mentioned by Ten Kate (2012), the fact that only a single case of a condition is currently seen in a family does not rule out the possibility that it is genetic, with maybe a significant recurrence risk. Many cases of severe autosomal dominant and X-linked conditions are new mutations, with no previous family history. Once the mutation has occurred, it can be transmitted through the family in an orthodox mendelian manner. Mutations are rare, so it is tempting to reassure the parent of a child with an apparently sporadic dominant condition that 'lightning is unlikely to strike twice'. But this would be wrong: it ignores the risk of germ-line mosaicism. This happens when a person is genetically normal at conception, but some time during development a cell in the germ line acquires a pathogenic mutation. The person ends up clinically normal but with a clone of mutant germ-line cells, so that they can produce recurrent mutant gametes, and recurrent affected children. If the pedigree shows a healthy couple having two or more affected children it may be misinterpreted as showing autosomal recessive inheritance. For the couple, this would not be seriously misleading because in either case the prediction is of a substantial recurrence risk (25 % if recessive, significant but hard to quantify if it is dominant). However, for an affected child, it is important to get the mode of inheritance right. If the condition were recessive, one would predict a very low recurrence risk (risk only if the person marries a carrier of the same condition), but if it is actually dominant the risk is 50 % (Fig. 1).

Fig. 1 The importance of not forgetting germ-line mosaicism. As discussed in the text, recurrence risks in this family are very different depending whether the condition is autosomal recessive or autosomal dominant with the father being a germ-line mosaic

Recessive conditions frequently present as a single case 'coming out of the blue', with no family history or consanguinity to indicate any risk. Correct counselling depends on recognising the condition and its mode of inheritance. Currently, that recognition depends on the skill and experience of the clinical geneticist. The new 'next generation' DNA sequencing technologies (Ropers 2012) make it possible to sequence every gene in an affected patient and, with luck, to identify the mutated gene without needing that clinical insight. Currently this is an expensive option, available only in research-based centres, but costs are falling very rapidly and the technology is quickly moving into diagnostic laboratories.

Making an accurate diagnosis of the family condition is an essential step in quantifying the reproductive risk. However, it also has important advantages in itself. Patients and their families whose conditions are undiagnosed can feel very isolated. Numerous studies have described the importance of a diagnosis, for patients and their families as well as for the clinicians and others involved in their care. Some of the benefits of making a precise diagnosis in a baby with birth defects include

- Providing accurate information about the condition, its natural history and its prognosis to parents and professionals involved in the care of the baby.
- Influencing the management of the baby—for example, it may direct further investigations or screening for complications.
- Facilitating accurate genetic counselling, especially as regards recurrence risk and possibilities for prenatal diagnosis.
- Making it easier for families to access support from other sources such as lay support groups, social services and the education system. Accessing such support usually involves filling in forms, one section of which, reasonably enough, asks for the diagnosis. If the parent is unable to give a specific diagnosis, it can be much more difficult to obtain necessary support.

The couple are from a population group with a high frequency of certain genetic diseases

Here we are concerned with genetic counselling and testing of persons who are at possibly increased individual genetic risk; the question of preconception screening, where subjects are not selected for any increased risk, is addressed by Metcalfe (2012). However, the distinction becomes blurred when a couple belong to an ethnic group where there is an increased frequency of certain conditions, but no population-based screening programme.

Such high population-specific risks are mainly seen with autosomal recessive conditions. For serious dominant and X-linked conditions where affected persons seldom reproduce, the frequency tends to be relatively uniform across populations. Natural selection rapidly removes the mutant alleles from the population, and the condition is maintained by recurrent new mutations. Mutation rates do not differ substantially between different populations, so these conditions occur largely sporadically and at roughly similar frequencies in all populations. Recessive conditions (and dominant late-onset conditions that do not inhibit reproduction) are much more likely to be population-specific. The high frequency may be seen in a whole population or just in a small group such as a clan or village. Sometimes the reason is natural selection, as in the high frequency of sickle cell disease and thalassaemia in populations exposed to malaria. In other cases, there is a founder effect: the population grew from a relatively small number of founders, one of whom happened to be a carrier of the condition. Among that person's many descendants, there will be many carriers of the condition.

Different ethnic groups have their own specific lists of frequent conditions. Where the carrier frequency is high and both partners are from the same group, it may be appropriate to offer carrier testing. Generally, only certain specific mutations in a gene are frequent in a given population, and this makes for quick and simple DNA tests. A negative test result will not exclude any other genetic risks, including the risk of the same disease but caused by a different mutation. However, it will reduce the risk for a couple from a high-risk ethnic minority to approximately the risk of the host population.

The couple is blood relatives (a consanguineous marriage)

Consanguinity is discussed in detail by Hamamy (2012). It is a delicate topic in genetic counselling. Consanguineous marriage increases the risk of having children with recessive disorders and from a genetic standpoint it unquestionably has disadvantages. In some populations, especially from the Middle East and the Indian subcontinent, high levels of parental consanguinity are common, and any general

discouraging of consanguineous marriages can easily be misinterpreted as racism. The genetic disadvantages must be weighed against the social advantages that may accrue from choosing a person known to all the family as a marriage partner in cultures where marriages are alliances invested with strong family honour and cemented by dowries. In such populations, it will be important to offer preconception screening for conditions that may be particularly frequent in that ethnic group, such as haemoglobinopathies.

Genetic consultations for consanguinity are more likely to come from members of populations where consanguineous marriage is unusual. In the native UK population, less than 1 % of marriages are between first cousins, and cousins contemplating marriage are likely to have been warned by friends or relatives of the bad consequences. Unless there is a family history of a specific recessive disease, the counselling would be that marrying your cousin roughly doubles the risk of serious problems. This can be presented either pessimistically, as increasing the risk from around 3 % to 6 %, or optimistically as only decreasing the risk of problem-free childbearing from 97 to 94 %.

The increased risk is of any of thousands of possible autosomal recessive conditions. In the past, it would have been impossible to offer any useful tests. With next-generation sequencing a genome-wide survey for recessive mutations is technically feasible. At present, this would still be far too expensive (in materials and skilled time) to introduce as a routine service, but costs are falling very rapidly and the time may soon come when such a service could be offered. Until then, when a recessive disorder is identified in one branch of a family and a cousin marriage is contemplated in another branch, then 'cascade testing' can be offered.

The couple is anxious about reproductive risks, even though there is no specific indication that they are at increased risk

Couples may be advised to come for preconception counselling. This is a valuable opportunity to offer general advice on healthy living and reproductive risks, to recommend participation in any relevant screening programmes, to recommend folate supplementation and so on. However, unless specific problems are identified, any advice given would be generic, rather than genetic advice tailored to the individuals. Probably, many lay persons believe they can have a genetic screen that will identify any possible risk—a supposition encouraged by some companies offering testing direct to consumers. It needs saying that in the absence of specific identifiable risk factors, genetic specialists can add little to the advice that primary care providers routinely offer to worried couples. Testing for a short list of common mutations would only give a spurious reassurance, as these are

unlikely to account for more than a small fraction of the total genetic risk in a population. Population-wide screening programmes may be setup to identify risk factors that are especially common in a certain population, but they can never deliver a general bill of good genetic health.

All this is changing with new technology. As described in this issue by Ropers (2012), ‘next generation’ sequencing technologies have revolutionised the scale of possible genetic investigations, and the revolution still has a long way to run. Costs are falling dramatically, and it is entirely likely that within a very few years it will be common for a person to have their entire genome sequenced. There are still some obstacles to using this as a routine screening tool. Typically a person has around three million DNA sequence variants compared to the standard ‘reference human genome’. The overwhelming majority of those will either have no effect whatsoever, or just be part of our general genetic individuality. Picking out potentially pathogenic changes is not easy, though as data accumulate about the variants carried by healthy people, it is getting easier. The risk remains that sequencing the DNA of a healthy person will identify a number of variants of unknown but possibly sinister significance, stoking anxiety without providing reassurance. There will need to be new forms of consent so that people have some choice about what types of result are revealed to them—not everybody would want to know if the analysis reveals a variant that will, or perhaps only might, lead to an untreatable disease, but some people will want to know, and somehow they must be empowered to decide in advance.

Acting on the knowledge

Once it is established that there is a reproductive risk, the question arises, what to do about it? As briefly sketched in this issue by Ten Kate a number of options are often available. Genetic counsellors (who may or may not be physicians, but who will always have specific training in genetics and counselling) need to help the couple fully understand their situation, and assist them in coming to their own decisions. People also have a right *not* to know, as long as not knowing does not harm anybody else. Geneticists must not force knowledge on to unwilling people.

Counselling is non-directive: the couple must arrive at their own fully informed decision, and the duty of the counsellor is then to support them, even if their decision is not the one that she herself would prefer. Such non-directive counselling can be stressful for a couple, who will often press the counsellor to say what she would do in their circumstances—but ultimately if their decision is their own, then even if it leads to disaster they are more likely

to accept their fate than if they had been talked into it by somebody else. Possible actions are discussed below.

Do nothing—let nature take its course

Some couples will opt for no medical intervention, despite identified risks. They may value the genetic service for the information and understanding it has given them, but not wish to take it any further. They might feel it is for God, and not them, to decide what happens, or they might dislike high-tech interventions in such intimate matters. Their decision must be respected.

Opt for preimplantation genetic diagnosis

Preimplantation genetic diagnosis is a highly specialised service involving the creation of embryos by in vitro fertilisation (IVF), then removing part of the embryo for genetic analysis. Usually, this is a single cell from a cleavage-stage embryo; alternatives are a polar body or a few cells from the trophoctoderm of a 5-day blastocyst. Ultra-sensitive techniques are needed to get reliable genotype information from a single cell, and the service is restricted to a few specialised centres. In principle, preimplantation diagnosis is possible for any monogenic condition where the pathogenic DNA variant has been identified by prior family study. It is not available for multifactorial conditions.

This targeted diagnosis of a specific genetic defect should not be confused with preimplantation screening of IVF embryos, where the aim is to select the best embryos for implantation in the absence of any known specific genetic risk. Preimplantation diagnosis is an established successful technique; preimplantation embryo screening is not. New approaches may offer better results, but 11 randomised controlled trials of current methods have failed to show any improvement in pregnancy rates resulting from such embryo screening.

Preimplantation diagnosis is sometimes presented as an easy ethical alternative to prenatal diagnosis. This is a very misleading view. It is expensive, very invasive because of the necessity to use IVF to get embryos for testing, stressful for the family and requires an exceptional level of skill and experience in the laboratory. In most countries access to this procedure is very limited, for instance because of its high cost.

Opt for prenatal diagnosis

Genetic disorders that cause structural abnormalities in the foetus can often be detected by detailed ultrasound examination. If it is necessary to obtain foetal material, the normal methods in current use involve either

chorion villus biopsy (CVB) at 10–12 weeks of gestation or amniocentesis at 14–20 weeks. CVB is usually the preferred option, both because it provides more foetal cells for DNA extraction or other analyses and because, if the test result is abnormal and the parents opt for termination, this can be done earlier in the pregnancy. However, it carries a rather higher risk of causing the pregnancy to miscarry (around 2 %, versus 0.5–1 % for amniocentesis; RCOG 2010) and there is a significant learning curve for the procedure, so that it is best done by an obstetrician who has already performed many such procedures.

Possible tests include DNA analysis, cytogenetic analysis by conventional karyotyping, fluorescence in situ hybridisation or hybridisation on microarrays, and biochemical tests. The latter might be performed either on the foetal cells or on cell-free amniotic fluid (for example to measure the concentration of alpha-fetoprotein as a test for neural tube defects).

Exciting new developments offer the promise of non-invasive prenatal diagnosis, with none of the risks or unpleasantness of amniocentesis or CVB. The blood of a pregnant woman contains both cells and free DNA of foetal origin. Attempts to isolate the foetal cells have not proved reliable enough to establish the technique as routine, but results with cell-free DNA are highly encouraging (Chiu et al. 2009). Foetal DNA is present in the maternal circulation from 4 weeks of pregnancy, and later may constitute 5–10 % of all the cell-free DNA in the blood. This allows reliable sexing of the foetus (using highly sensitive techniques to look for the presence of DNA from the Y chromosome) and is also routinely used for checking for rhesus incompatibility. The DNA can be used for genetic diagnosis of any mutation of paternal origin. Mutations that might be inherited from the mother are masked by the large excess of maternal DNA in the blood, but it has been shown that in principle these, and also numerical chromosome anomalies such as trisomy 21, can still be detected by careful quantitative analysis of the DNA.

Whatever the technique, it is important that women are not pressured into terminating a pregnancy if the results indicate an abnormality. Many will want to do so, but some will request prenatal diagnosis so that they can prepare themselves for the birth of an abnormal baby, and their right to do this must be respected.

Other reproductive options

Some couples will prefer not to take a reproductive risk, and may choose to use donor eggs or sperm, to adopt, or simply not to have children. All these options should be presented during counselling, so that the couple can make their personal decision knowing the full range of options open to them.

Concluding remarks

Couples may be at actual or perceived increased genetic risk for a variety of reasons. The first task of both the primary care team and the geneticist is to establish the facts, make any necessary diagnoses and determine what, if any, increased risk there is. We are currently in a period of breakneck technical development. The range of circumstances where genetic testing can be useful is about to undergo major expansion, with the ability to identify genetic risk factors even in the absence of any specific indications. These new abilities will require new forms of informed consent and will likely change the way clinical geneticists work.

However, once the facts have been established, the human business of counselling will continue much as now. Following a widely accepted definition produced by the American Society of Human Genetics, the counselling process must help the individual or family to

1. Comprehend the medical facts, including the diagnosis, probable course of the disorder, and the available management
2. Appreciate the way heredity contributes to the disorder, and the risk of recurrence in specified relatives
3. Understand the alternatives for dealing with the risk of recurrence
4. Choose the course of action which seems to them appropriate in view of their risk, their family goals and their ethical and religious standards, and to act in accordance with that decision
5. Make the best possible adjustment to the disorder in an affected family member and/or the risk of recurrence of that disorder

The book by Harper (2010) is recommended for detailed discussion of counselling issues and the books by Bradley-Smith et al. (2009) and by Firth and Hurst (2005) are useful sources for quick reference.

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