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Children in Genetic Research

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Advanced Article
(Advanced articles are aimed at advanced undergraduates, graduate students, postgraduates, and researchers reading outside their field of expertise.)

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Abstract

Genetic research offers potential benefits and harms to children. Respect for children's individual and collective best interests, and for their human rights and worth and dignity includes keeping them informed, and involving competent children as much as possible in making decisions about genetic research that affects them. Their privacy and identity must be respected, as well as the consent or refusal of parents and of competent children. The article reviews the *Declaration of Helsinki* and other ethical guidance, as well as differing standards for research with children between Britain and the USA. The term 'therapeutic research' is critically analysed, and also questions of justice and who bears the burdens or enjoys the benefits of genetic research in richer and in poorer countries. Research with children about dominant and recessive, autosomal and sex-linked genetic conditions, about multi-genetic predisposition meaning causally heterogeneous and often complex in origin, genomics and epigenetics, gene therapy and nature versus nurture, ADHD and economic influences is discussed.

Key Concepts:

- Genetic research includes investigation into how children's traits, anomalies, behaviour or disease might be influenced by genomics, or by epigenetics, how this knowledge can be applied and shared, and how interventions to detect, treat and prevent adverse genetic conditions can be developed.
- Research ranges from the study of conditions associated with single genes in closed predictable systems, to multi-genetic predispositions interacting with many environmental influences.
- The differing influences of genes and environment and their complex overlapping and interactions are debated, particularly regarding behavioural conditions.
- When exploring connections between genotypes and phenotypes (ways in which genes are expressed) researchers also need to know about children's social contexts.
- There are risks that genetic researchers overstate the value and influence of their knowledge on health, and confuse giving information with providing therapy.

- Children and adults tend not to accept advice to alter their life-style significantly in order to reduce or prevent symptoms of a genetic condition.
- Research about gene therapy incurs risks and has not yet provided tested or proven effective treatments.
- Children should be involved in genetic research only if the findings are intended to benefit them and cannot be obtained from an older age group.
- Economics crucially influences all stages of genetic research in the selection of topics, the funding and scale of projects, promotion of reports, and implementation of findings.
- Social justice requires that the groups of children who take part in research, including those in poorer countries, should also be able to benefit from the findings.

Introduction

Genetic research covers scientific, medical and social research about the causes, nature and effects, diagnosis, prevention and treatment of genetic conditions, and about people's views and experiences of genetics. While genetic research promises great potential benefits, it can also raise problems for children. This article reviews the present state of genetic research with children and the guidance to protect and respect them. The topics to be discussed include: confusions about 'therapeutic research', and between giving information and giving therapy; the expansion of genetics towards epigenetics and interactions between genes and environment; problems of definition, measurement and prediction in genetic research; ethical standards set by the *Declaration of Helsinki* (WMA, 2000) and other guidance and law on children's rights, evaluating risks and benefits, respecting consent and privacy; when to involve children in research; economic influences; and some of the effects of genetic research on children.

'Therapeutic Research'?

Research is systematic investigation. This basic definition is important, because the history of medical research has been confused by the concept of 'therapeutic research' (US National Commission, 1977). 'Therapeutic' describes treatment that is beneficial and not harmful or useless. However, 'research' as investigation is not treatment, and so does not directly benefit the people being investigated; indeed, these people benefit the research. The research findings may in future benefit countless people, but this hope links to another confusion associated with 'therapeutic research'. Ethics guidelines allow research when the higher the hoped-for benefits, the higher are the permitted risks (RCPCH, 2000). This guidance is often taken to mean benefit to the person being researched. Yet since research itself cannot benefit the person, the actual equation is risk to the person versus benefit to society.

'Therapeutic research' tests a treatment, but whether that treatment does more good than harm, or does more good than other treatments, are questions for the research to investigate. They are not certainties, and talk of 'therapeutic research' can mislead doctors and patients into believing that taking part in the research offers the best or only hope for them. This prevents people from being able to make a fully informed and balanced decision based on equipoise, which is 1) the belief that refusing or consenting to join any option in a research program offers an even

chance of benefit and risk, or 2) at least if there is felt to be an imbalance, this has not yet been proven.

Since 1964, the series of versions of the *Declaration of Helsinki* (WMA, 2008) has been the international guide to ethical standards in research. Medical research ethics committees and journals should only approve or publish research that observes *Helsinki* standards which clearly separate research from treatment, avoiding the fuzzy overlap of 'therapeutic research':

> 'Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects' (WMA, 2008, clause 21).

Helsinki states that research aims 'to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments)...for their safety, effectiveness, efficiency, accessibility and quality' (WMA, 2008, clause 7). Therapy is distinguished here from diagnosis. Patients may see diagnosis as necessary but not sufficient for therapy. If doctors say, 'We have diagnosed this fatal disease, but we do not yet know how to prevent or treat it', or 'the treatment is too expensive', then the diagnosis alone will not feel therapeutic.

Genetic Information and Therapy

Geneticists, however, frequently describe providing information, diagnoses and counselling as therapy. For decades, regional genetic services gradually attracted considerable funding and support, mainly by offering information that they collected through family case histories; in effect, they were research rather than treatment centers (Coventry and Pickstone, 1999). There is concern that blurred boundaries between healthcare and research in genetic clinics may mislead families into expecting to receive care, whereas the session may mainly involve collecting data from them that might help towards developing future services (Ponder, et al., 2008). See also: DOI: 10.1002/9780470015902.a0005623.pub2.

Genetic research can raise very high hopes among affected families, and is largely supported through their fund-raising efforts, as their self-help organisations' websites show. Partly to promote continued support, the websites and media press releases tend to emphasize 'miracle breakthroughs' in genetic research, and repeated promises of effective therapy 'in five years' time'. However, as some acknowledge (for example, www.Genomics.energy.gov), so far gene therapy on humans has been experimental and not yet proven to be successful in clinical trials. There has been little progress since 1990, with setbacks after the death of a few child patients. Unresolved problems include: the short-lived effects of therapy and therefore the need for repeated treatments; patients' immune responses that destroy the invading gene; dangers to the patient from the viral vectors used to transmit the inserted gene; and the fact that most conditions are multi-genetic ones, which single-gene treatments may not be able to ~~cannot~~ help.

The extent to which children and/or their parents will agree to harmful research is illustrated by the boys with life-limiting Duchenne muscular dystrophy who had 50 myoblast injections into one leg, and 50 placebo injections into the other (Gussoni *et al.*, 1992). The report did not mention the boys' pain, dashed hopes and possible sense of having being deceived into giving consent to unsuccessful research. Efforts

continue today. The Children's National Medical Center Washington DC website (CNMC, 2011) explains their Duchenne gene therapy research involving intramuscular injections, and invites parents to contact them.

Risk–benefit equations, which assume that nothing can be worse than the untreated disease, could permit interventions which increase children's suffering and even shorten already brief lives. 'Risk' covers expected and unpredicted harms, costs and inconveniences. Although risk probability and frequency can be measured, risk severity is often a personal assessment, so that it is vital that the child undertaking the risk is informed and involved as fully as possible in decisions (BMA, 2001).

In 2003, the Human Genome Project completed and stored the sequencing of approximately 20,000-25,000 genes and the three billion chemical base pairs that make up human DNA (HGP, 2011). See also: DOI: 10.1002/9780470015902.a0003446.pub2. Work continues on an almost infinite task of tracing connections between genotypes (genes that encode proteins) and phenotypes (ways in which genes are expressed in traits and behaviours). For example, six new genetic variants were linked to type II diabetes in people with South Asians origins. In the past few years, children and young people in Britain have been developing type II diabetes, a disease once associated with middle to old age. As usual, the report of this new knowledge from the 'largest international collaboration ever undertaken in biology' promises to 'lead the search for diagnostic markers and drug targets to prevent and treat this major disease' (Wellcome, 2011).

So far, genetic treatments have mainly been tested in animals. For instance, researchers reported correcting the genetic sickle cell disease in adult mice (NIH, 2011). Sickling (alteration of the normal biconcave disc shape of red blood cells into a sickle shape) increases after birth, with painful, disabling and sometimes fatal results. In sickle cell, soon after birth, the protein BCL11A suppresses the production of the healthier foetal haemoglobin (the protein in red blood cells that contains iron and carries oxygen round the body). Scientists blocked BCL11A by 'silencing' the genes that produce it, so that the healthier foetal kind of haemoglobin could continue to be produced instead. They hope that their discovery will, one day, translate into effective therapies. Meanwhile, there are long processes of translating knowledge and techniques from lab bench discovery into bedside treatment. See also: DOI: 10.1002/9780470015902.a0005208.pub2.

A first step towards developing new treatments is to identify the genetic activity. In research on ADHD, attention deficit hyperactivity disorder, Martel et al. (2010) 'examined whether the dopamine receptor D4 (DRD4) Promoter 120-BP10 repeat polymorphism gene, previously associated with ADHD, moderated the effects of inconsistent parenting and marital conflict on ADHD or oppositional defiant disorder'. Participants who gave genetic samples for analysis, included over 500 children with ADHD, non-ADHD comparison children, and their parents. The researchers found that

> 'homozygosity for the DRD4 Promoter 120-BP10 repeat insertion allele increased vulnerability for ADHD and oppositional defiance only in the presence of inconsistent parenting, and appeared to increase susceptibility to the influence of increased child self-blame for marital conflict on ADHD inattention. [They concluded:] DRD4 genotypes may interact with these

> proximal family environmental risk factors by increasing an individual's responsivity to environmental contingencies.'

The word 'may' in the final sentence denotes that no clear evidence was found. As Baughman and Covey (2006) point out, ADHD has not yet been diagnosed by a definite genetic, anatomical or hormonal sign. Millions of children have medication for ADHD, and it is uncertain whether data from behavioural observations or from neuro-scans are either evidence of ADHD or of the effects of the medication. Further, ADHD is a vague set of fluctuating behaviours that are highly affected by contexts and beliefs. In rural African areas with no powered machinery, 'hyperactivity' can be life-giving muscular energy, which is essential for everyday subsistence survival. Yet the authors imply that hyperactivity, as well as 'inconsistent parenting', 'marital conflict' and 'oppositional defiant disorder' (this may mean a 2-year-old saying 'no'), can be identified precisely, accurately and uniformly. They also imply that families can be divided into specific groups: those that always have these behaviours and those that never have them. This ignores blurring overlaps, variations and subjective assessments of many possible, inextricably interacting causes and effects.

The most effective gene therapy might be to alter genes at or before conception before the genetic condition develops and multiplies through the cells. However, international Conventions (UNESCO, 1997) reject biotechnological attempts to alter the genomes of future human generations through altering the gametes. That would violate basic human rights (UN, 1948, 1989; Council of Europe, 1997, 2004a) if it created a higher, gene-rich class of people.

> 'The genetic diversity of humanity must not give rise to any interpretation of a social or political nature which could call into question the inherent dignity and...the equal and inalienable rights of all members of the human family'

(UNESCO, 1997), and see European College Court of Human Rights (1997), European Commission (2004a), which set ethical conditions for genetic research.

Social Justice in Genetic Research

Helsinki further aims to prevent research from being done in poor countries, which will develop treatments only to be provided in rich countries (and see Teck-Chuan, et al., 2008).

> '17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
> 18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

> 19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research' (WMA, 2008).

An example from Nigeria illustrates complications of international genetic research with children (Sun News, 2011). Researchers at the University of Benin Teaching Hospital in Nigeria reported:

> 'a major scientific breakthrough in having a successful stem cell transplant on a patient with sickle cell anaemia. This is, indeed, good news...The feat, which was performed on a seven-year old sickle cell anemia patient, who had suffered stroke...The breakthrough was achieved through a one-year training collaboration [with a Swiss university]. The transplant, which would cost between N2.5 million and N5million for a patient locally and even N25 million abroad, cost the hospital N2.1 million on drugs alone for the first beneficiary. [The report congratulated all the researchers, the university] the Presidency and the federal health authorities [for providing the training and the staff. The] feat has given hope that something good can still come out of our "Centres of Excellence" despite the deplorable condition of the nation's health sector occasioned by poor funding, dearth of continuous medical education and equipment.'

Government, business and philanthropists were exhorted to fund further stem cell projects. The boy's brother had donated the stem cells, thus overcoming ethical problems of using foetal stem cells.

Sickle cell affects hundreds of thousands of people very seriously and is a huge burden on nations' economy and services, as well as causing enormous personal suffering among Black, Asian and Mediterranean peoples. Effective treatments are urgently needed. However, informed public support for research, and the basic healthcare rule 'do no harm' are undermined when, as in the Nigerian-Swiss example: tentative, uncertain, early results are presented as triumphant achievements (note the number of positive terms in the above quote); pioneering work that should first be tried with informed, willing adults is conducted on young children; research is conducted in poorer countries, which might not be allowed in wealthier ones with their stricter rules on ethics and consent; researchers try to develop immensely expensive treatments, which only a tiny number of people will be able to afford, and which drain funds, staff-time and training, and resources away from much cheaper, effective healthcare that can help millions of people and is so desperately needed in Africa. The experiment ignores many standards in *Helsinki.*

Vital as *Helsinki* clauses 17-19 are, they raise problems for families with a genetic condition. The standards could require that when treatments are being investigated, say for sickle cell, all the research from early trials to test toxicity onwards should only be done with affected families. If 'healthy volunteers' (non-patients) are needed, they might have to be the siblings of children who have sickle cell, who 'stand to benefit' if their relatives might be helped by the future treatment. This argument could increase the already heavy burden on affected families, and prevent others from altruistically supporting them. It illustrates the complications of setting, interpreting and applying important general ethical standards.

From Genomics to Predisposition to Epigenetics.

The study of specific genes in dominant or recessive genetic conditions (see glossary) has moved on to the more commonly occurring complex interactions between several genes, and how these can increase the predisposition of an affected person to develop a full condition. Examples of predisposition include diabetes, which may or may not run in families. Type II diabetes is linked to life-style, diet and lack of exercise, and is increasingly seen in younger as well as older people. Type I diabetes begins in childhood, although often in children who are fit, slim and active, and it might be linked to genetic vulnerability to an infection, which causes the pancreas to stop secreting insulin.

Epigenetics (see glossary) further complicates the original study of genetics to track specific genes. For example, researchers observed that children born to the daughters of men who, as children in the nineteenth century, had faced tough times (severe malnutrition) have been found to be at above average risk of adult-onset complex disorders such as hypertension, diabetes type 2 and coronary artery disease ~~paternal (but not maternal) grandsons of Swedish men who were exposed during preadolescence to famine in the nineteenth century were less likely to die of cardiovascular disease. However, when food was plentiful, the grandchildren were more likely to die from diabetes~~ (Pembrey et al., 2006). The ~~opposite effect was observed for females—the paternal (but not maternal)~~ granddaughters of women who had experienced famine while they were in the womb (and therefore while their eggs were being formed) lived shorter lives on average.

Genes Versus Environment

Large research projects on birth cohorts of children aim to unravel the origins and causes of their characteristics, behaviour and health in features as basic as height and weight, and to attribute proportional influences to genetics or to environment. One example is the ALSPAC Avon study in Western England of babies born in 1990, and which reported identifying a gene related to a tendency to be overweight (http://www.bristol.ac.uk/alspac/).

Another favoured research method is to study twins and to measure the supposed percentage influence of genetics versus environment. Separated twins, such as those who are adopted, are valued in these studies, since twins living together share so much of their nurture as well as their nature, more than their other siblings because of their common age, position in the family, shared fetal lives and other circumstances that may last throughout childhood (Plomin and Spinath, 2004). Yet given how much siblings, including twins, can also differ from one another, some analysts argue that nurture in terms of children's peers and wider socio-economic environment should also be researched extensively. Evolutionary psychologist Steven Pinker (2002) contrasted nurture in culture that influences choice of a child's language or religion, versus genetic traits, which he considers influence children's temperament, their proficiency with language, or how religious or liberal or conservative they might be. Pinker considers that it is feasible to measure the heritability of a trait, the percentage proportion of nature or nurture, although not in individuals but in the degree of variation between individuals in a population. Pinker's multivariate genetic analysis examines the genetic contribution to several traits likely to interact, such as for memory, spatial reasoning and processing speed. He considers that genes affecting scholastic achievement and cognitive ability completely overlap.

The biologically dominated approach to research about the possible social effects of genetics has its critics among geneticists, biologists, philosophers and social scientists (for example, Harper and Clarke, 1997; Clarke, 1998; Rose and Rose, 2000). They say that the influences of nature and nurture are too complex and subtle for researchers to be able to separate or measure them distinctly, given the numerous overlaps, interactions and mutually modifying effects. Overly biological, reductionist and quantitative research assumes that genetic data are definitive rather than frequently being elusive and uncertain. The research also treats genetics as if it is a closed system, mentioned earlier, when one cause invariably has one predicable effect, free from all other influences, which is rare in the natural world and unknown in the social world. Here, open systems combine personal, interpersonal, economic and political interactions, processes, and constant change through social structures as well as individual agency (Bhaskar and Danermark, 2006). Genes linked to obesity, for example, cannot wholly explain the recent massive international rise in rates of obesity. And genetic research connected with behaviour raises troubling moral questions about the extent of free will versus genetic determinism or overwhelming influence. This is especially complicated in research with children, which explores powerful adult influences in their early life as well as their emerging moral awareness and autonomy (Alderson, 2008). Many research and clinical geneticists explore the complicated interactions between genetics and environment. 'The taking of a family history in the genetic clinic obtains vital information about many factors that influence children's lives and modify the risks of genetic disease, which genome sequence data alone cannot provide' (Clarke, 2009).

Global funding for genomics is approaching $3billion a year. However 'genomycism' or overestimations of the accuracy and predictive power of genome sequencing has been criticised as 'unrealistic, overinflated, and over-hyped' and geneticists call for more realistic research and application in the clinic (Evans, et al., 2011; Witten, 2011; see also Marteau, et al. 2010). They want less emphasis on low risk conditions, on small differences in risks for common conditions, and on advising ambitious behavioural changes of diet and life-style because people rarely achieve these. Genetic information should be more accurate and reliable, and research and funding priorities and promises should be more realistic, they consider.

Research Ethics

The risks and hoped-for benefits of genetic research affect all age groups but especially children, both in their present vulnerable dependence and in potential long-term effects over their future decades of life. Genetic research and the services that it supports and expands raise ethical questions, some of which are reviewed in this section. What is an abnormal disability or disorder, or alternatively what is part of the spectrum of normality? Who defines normality and on what basis? (Burke et al., 2011). My research repeatedly found that seriously impaired children described themselves and their lives as 'normal'. Either they expanded concepts of normality to include themselves or they took their daily life with all the restrictions and rewards for granted. For instance, a~~A~~lthough her body was wasted and twisted by anterior horn cell damage and scoliosis, leaning on her crutches 11-year-old 'Niki' insisted, ~~like other disabled children I have interviewed,~~ 'It's so important to be normal,' by which she meant going to mainstream school, enjoying life with her family and friends, and planning when she was adult 'to go out into that big wide world and do what normal people do' (Alderson, 1993, p.125).

There are also questions about whether we should try to cure or prevent all disabilities. Some adults with a genetic condition, such as sickle cell or Thalassaemia, argue that efforts to identify and terminate all pregnancies that are likely to be affected by their condition involve dangerous discrimination and even a form of genocide (Alderson, 2002). There is a double standard in efforts to apply research that has identified genes for specific conditions, when . Ffor older people, 'therapy' usually involves advice about life-style to help them to reduce or prevent symptoms, whereas . However prenatally, 'therapy' or 'prevention' tend to be the opportunity to terminate an affected pregnancy. If parents decide to continue the pregnancy, and their child has a genetic condition requiring expensive treatment such as cystic fibrosis, in countries with private health services some insurers refuse to fund treatment, arguing that the parents must pay because they deliberately chose not to have prenatal screening and termination. Prenatal screening can then increase discrimination against genetically impaired people. See also: DOI: 10.1002/9780470015902.a0005208.pub2.

Genetic research can involve developing technologies, such as a new non-invasive prenatal test for Down syndrome. This is , reported to detect 98.6 percent of affected foetuses, with a false positive rate of 0.2 percent. Commercial The promotion by the company avoids mentioning that the intention of the tests is to offer potential parents the option of terminating the pregnancy, and ignores evidence about the high quality of life for many children with Down syndrome and their families. One That company was recently found guilty of inflating its share prices by over-estimating the accuracy of another test for Down syndrome (Cook, 2011a).

A further economic ethical problem is that early attempts at gene therapy are exorbitantly expensive, as in the earlier Nigerian example. Who will have access to them and who will pay for them?

There is also the risk that children and parents may be coping well with a condition until a newly found genetic link is publicised, which could potentially medicalise the condition, and increase their anxiety and dependence on medical help.

Another risk is inadvertently to excuse or endorse unhealthy behaviours. For example, the impact of being asked to attend an obesity clinic in a large children's hospital convinced one mother that her son's obesity was a genetic illness. The hospital context counteracted the doctor's gentle insistence that the cause was behavioural (frequent snacks, large portions, little exercise). The mother continued to be certain that a genetic cause and cure would be found and meanwhile, until he could have the medical 'cure'technical fix, she must 'treat' her son's illness by increasing the portions and pushing him to school in a wheelchair. See also: DOI: 10.1002/9780470015902.a0003473; DOI: 10.1002/9780470015902.a0005892.pub2

Alan Petersen (2011) reviews whether bioethics is too ready to follow and support genetic research and innovations, instead of more critically analysing their actual benefits and costs to society.

Consent

The Convention on the Rights of the Child (UN, 1989, Article 12) enshrines the child's right at any age to express a view 'in all matters affecting the child' and for 'due weight to be taken' of these views. English case law respects the legally valid consent of competent children, age is notto specified (*Gillick* v. *Wisbech and West*

Norfolk Area Health Authority [1985]). Competence includes understanding proposed interventions, evaluating information, making a wise decision in the child's interests, or at least not against those interests (RCPCH, 2000), and accepting responsibility – not blaming others, if predicted risks turn into actual harms. Besides the child's own capacities, adults' clear information, support and respect for children affect their competence. Some children aged 6 or 7 years, during lengthy illness and treatment, are believed by adults caring for them to be able and willing to consent to major treatment, making decisions that few healthy children would understand (Alderson, 1993). Standards for consent to medical research are higher than those regarding treatment. Parents' consent should also be requested, and even young children's refusal should be respected (US Commission, 1977; RCPCH, 2000). It is harder for adults and children to make informed decisions about extremely complex new knowledge and genetic conditions beyond their experience, so they need very clear spoken and written information. Essential information includes explaining the research 'aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks...and discomforts...and any other relevant aspects of the study' (WMA, 2000, clause 24). These might include explaining research terms such as 'randomise', and also 'the right to refuse or to withdraw consent at any time without reprisal' (WMA, 2000: clause 24); and to ask questions and have time to reflect.

One view is that informed consent dangerously delays medical research and we should not be 'freeloaders' who benefit from research but do not contribute ourselves. Therefore, by law, we should all take part in research, perhaps every ten years when we could choose our research project, which would partly respect consent. The opposite view is that we must fully respect everyone's bodily integrity and freedom of choice. A recent debate at the University of Minnesota was complicated by two matters. In 2003 a young man committed suicide there while in a clinical trial of an antipsychotic drug. There was also concern that most research centres will not pay for research subjects' lost wages, their suffering or their health care bills if something goes wrong (Cook, 2011b). This last argument applies less in Britain where NHS services are free at present. Pete Shanks (2011) contrasts the new pressures that everyone should volunteer to take part in research, with the very high profits made by pharmaceutical companies and some medical researchers. In the past 30 years, more than 40,000 patents have been granted on genes alone (Washington, 2011). University researchers used to collaborate and share new knowledge freely, but now they compete for profit. Researchers' close relationships with pharmaceutical and biotechnology companies increase the risks that biased misinformation will be given to potential research participants, to the public, and also in final research reports.

Genetic research involves 'immortal' stem cell-lines, and databanks holding children's DNA and personal details, which are hired out to numerous research teams around the world. Although ethics committees may vet the original purposes of each research project, no one can predict or therefore fully consent to all the possible uses and outcomes. And children's rights may be overlooked. Iceland has a national opt-out genebank, deCODE; every newborn child is enrolled unless the parents know that they can opt their child out and decide to do so. If they do not, the children themselves cannot withdraw until they are 18, and they cannot withdraw their data retrospectively (Rose, 2001). Brown and Webster (2004) considered the growing institutional, legal and economic networks and markets, and the future

technologies of social control, surveillance, informatics, biomedical engineering, new hybrids and warfare that genetic databanks may serve, through as yet unknown technical and social processes. Consent is supposed to have a direct link between the gift of research data ('data' meaning given) and the donor's intellectual and moral prospective control over the specific use of data, but this control is dispersing elusively across the many potential secondary analyses by unknown future research teams well beyond the foreseeable future~~is timeless diffusion~~. See also: DOI: 10.1002/9780470015902.a0020655.

Confidentiality

The 1998 *Human Rights Act* Article 8 respects everyone's right to 'private and family life', which relates to genetic identity in complicated ways. Research subjects' right to safeguard their integrity must always be respected.

> 'Every precaution should be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity' (WMA, 2000, clause 23)

Children's rights to genetic privacy can be undermined if relatives think they have a right to knowledge about their 'common gene pool'. Before knowledge about a child's genetic status is shared with the child, with parents and other relatives, or is given, anonymously or not, to third parties for research or commercial use, the risks should be considered carefully.

When Is It Appropriate To Involve Children In Genetic Research?

The first international guidance excluded children from medical research (*Nuremberg Code*, 1947). Guidance gradually included children, so that they were not left as 'therapeutic orphans' with untreatable childhood conditions (US National Commission, 1977). Researchers must protect the interests of all their research subjects. *Helsinki* (WMA, 2008, clauses 17, 22, 26-29) discusses extra protections for groups such as children. A British report (Clothier, 1992) reviewed how gene therapy involves immensely complex techniques, uncertainties and dangers. The 'correcting gene' might be inserted into the wrong cell type, inappropriately, in the wrong amount, or at the wrong time during development. It might move into other genes, creating unwanted effects. Changes in one gene might inadvertently affect other genes, initiate cancerous growths or new genetic disease, or have other unknown longer-term effects. Yet the report advised that the 'first candidates' for gene therapy (including experiment) will preferably be treated 'in early childhood and even before birth'.

Most guidance, however, sets higher standards. While new treatment is being developed, it is tested first in Phase I trials to check whether it often has harmful effects, then in small~~er~~ Phase II trials for effectiveness. Phase III involves large randomised controlled trials, before drugs are licensed and allowed for general use. Children are affected by differing ethics guidance about clinical trials. The USA allows research protocols in which: first, children are enrolled alongside adults simply to increase numbers of research subjects; second, no separate data collection on different age groups is required; third, new treatments can be tested against placebos or dummy treatments (DHHS, 1991: Ross, 1998). In contrast, in Britain and

Europe research ethics committees must require higher standards (European College, 1997; RCPCH, 2000; BMA, 2001; MRC, 2004; European Commission, 2004b; WMA, 2008, clause 27); first, that research can only be done with children if it cannot be done with adults, and then, for example, research to test doses for younger age groups should whenever possible follow research that has been done with adults. Second, children may be involved only if the research is intended to benefit their age group, and therefore separate data must be collected and analysed for each age range. Third, new treatments are tested against the best available current treatment, and not against placebos, when the new treatment is likely to look more effective than it might really be. There is concern that the European Commission guidance (2004b), which addresses only parents' and not also children's consent, overrides competent children's views and English *Gillick* law [1984] and guidance (RCPCH, 2000; MRC, 2004; DH, 2005) which respects competent children (Biggs, 2009; Alderson and Morrow, 2011; Brazier and Cave, 2011). Proposed gene therapy research has first to be approved by the UK Gene Therapy Advisory Committee and the final decision to take part must rest with the child's and/or parents' informed and voluntary (willing and unpressured) consent. Ethical problems continue to arise, See also: DOI: 10.1002/9780470015902.a0005589.pub2.

Effects of Genetic Research on Children

Ethical guidance concentrates on protecting research subjects during data collection. The potential impact on children during subsequent publicity and use of research findings is also crucial. For example, social research on children's views about genetics could either demean them, if it concludes that they do not and cannot understand, or else could emancipate them through showing their capacity to understand and reflect when they are clearly informed and involved in respectful discussions. With the current gap between increasing genetic knowledge and lack of treatments for genetic conditions, as discussed earlier, termination of pregnancy is the most common 'treatment' after diagnosis. This may benefit families who would have had a severely impaired child. Yet genetic research can raise expectations of parents' 'rights to have a designer baby' (Parens, 1998), which increase intolerant exclusion of disabled and disturbed children, and can divert funds away from medical and social support for them (Shakespeare, 1998). Genetic research powerfully influences society's values and choices and these in turn, with economic pressures, shape the course of genetic research.

~~**[Note from author –** I have inserted 41 references, and 18 further reading, which are ethical guidelines. Would it be better to combine them?]~~

References

- Alderson, P. (1993) *Children's Consent to Surgery*. Buckingham, UK: Open University Press.
- Alderson, P. (2002) Prenatal counselling and images of disability, in Dickenson, D. (ed.) *Ethical Issues in Maternal-Fetal Medicine.* Cambridge: Cambridge University Press, pp. 195-212.

- Alderson, P. (2008) *Young Children's Rights.* London: Jessica Kingsley.
- Alderson , P. (2007) Competent children? Minors' consent to health care treatment and research. *Social Science and Medicine,* 65:2272-2283.
- Alderson, P. and Morrow, V. (2011) *The Ethics of Research with Children and Young People.* London: Sage.
- Baughman, F. and C. Covey. (2006) *The ADHD Fraud: How Psychiatry Makes Patients out of Normal Children.* Bloomington IN: Trafford.
- Biggs, H. (2009) *Healthcare Research Ethics and Law*. London: Routledge-Cavendish.
- Bhaskar, R. and Danermark, B. (2006) Metatheory, Interdisciplinarity and disability research: a critical realist perspective, *Scandinavian Journal of Disability Research,* 8,4:278-297.
- Brazier, M. and Cave, E. (2011) *Medicine, Patients and The Law*. Fifth edition. London: Penguin.
- Brown, N. and Webster, A. (2004) *New Medical Technologies and Society: Reordering Life.* Cambridge: Polity.
- Burke, W., Goering, S., Fryer-Edwards, K., Holland, S. and Trinidad, S. (eds.) (2011) *Achieving Justice in Genomic Translation: Rethinking the Pathway to Benefit.* New York: Oxford University Press.
- Clarke, A. (ed.) (1998) *The Genetic Testing of Children*. Oxford, UK/Washington, DC: Bios.
- Clarke, A. (2009) Musings on genome medicine: the value of a family history, *Genome Medicine*, 1, 8:75.
- CNMC - Children's National Medical Center Washington DC (2011) http://www.childrensnational.org/research/OurResearch/TranslationalResearch/CGMR/MuscularDystrophy.aspx
- Cook, M. (2011a) Non-invasive Down syndrome test available next week. http/www.genomeweb.com.
- Cook, M. (2011b) Are we morally obliged to participate in research? http/www.genomeweb.com. .
- Coventry P and Pickstone J (1999) From what and why did genetics emerge as a medical specialism in the 1970s in the UK? *Social Science and Medicine,* 49:1227–1238.
- Evans, J., Meslin, E. Marteau, T. and Caulfield, T. (2011) Deflating the Genomic Bubble, *Science,* 331, 6019: 861-862.
- Gussoni, E., Pavlath, G. and Lanctot, A. (1992) Normal dystrophin transcripts detected in Duchenne muscular dystrophy patients after myoblast transplantation. *Nature,* 356:435–438.
- Harper, P. and Clarke, A. (eds.) (1997) *Genetics, Society and Clinical Practice*. Oxford, UK/Washington, DC: Bios.
- HGP - Human Genome Project information (2011) http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml.
- Marteau, T., French, D., Griffin, S., Prevost, A., Sutton, S., Watkison, C, Attwood, S. and Hollands, G. (2011) Effects of communicating DNA-based disease risk estimates on risk-reducing behaviours. *Cochrane Database of Systematic Reviews*. 2010; issue 10 Art. No.: CD007275. DOI: 10.1002/14651858.CD007275.pub2.
- Martel, M., Nikolas, M., Jernigan, K., Friderici, K., Waldman, I., and Nigg, J. (2010) The dopamine receptor D4 gene (DRD4) moderates family

environmental effects on ADHD, *Journal of Abnormal Child Psychology, 39*, 1-10.

- NIH- National Institutes for Health. (2011) *Protein could be a target for treating people who have the blood disorder* http://www.nih.gov/news/health/oct2011/nhlbi-13.htm
- Nicholson, R. (ed.) (1986) *Medical Research with Children: Ethics, Law and Practice.* Oxford, UK: Oxford University Press, pp. 76–124.
- Parens, E. (ed.) (1998) *Enhancing Human Traits: Ethical and Social Implications*. Washington, DC: Georgetown University Press.
- Pembrey, M., Bygren, L., Kaati, G., *et al.* (2006) Sex-specific, male-line transgenerational responses in humans. *European Journal of Human Genetics,*14: 159–66.
- Petersen, A. (2011) Can and should sociology save bioethics? *Medical Sociology News,* 6, 1:2-14, www.medicalsociologyonline.org
- Pinker, S. (2002) *The Blank Slate: The Modern Denial of Human Nature.* London: Allen Lane.
- Plomin, R. and Spinath, F. (2004). Intelligence: genetics, genes, and genomics', *Journal of Personality and Social Psychology,* 86,1:112–129.
- Ponder, M., Statham, H., Hallowell, N., Moon, J., Richards, M. and Raymond, F. (2008) Genetic research on rare familial disorders: consent and the blurred boundaries between clinical service and research, *Journal of Medical Ethics,* 34,9:690-
- Rose, H. (2001) *The Commodification of Bioinformation: The Icelandic Health Sector Database.* London: Wellcome Trust.
- Rose, H. and Rose, S. eds. (2001) *Alas Poor Darwin: Arguments against Evolutionary Psychology.* London: Verso.
- Ross, L. (1998) *Children, Families and Healthcare Decision Making*. New York: Oxford University Press.
- Russo, V., Martienssen, R. and Riggs, A. (1996) Epigenetic Mechanisms of Gene Regulation. New York: Cold Spring Harbor Laboratory Press.
- Shakespeare T (1998) Choices and rights: eugenics, genetics and disability equality. *Disability and Society* **13**(5): 665–681.
- Shanks, P. (2011) Moral obligations for thee but not for me? www.geneticsandsociety.org
- Sun News (2011) Nigeria's first stem cell transplant. http://www.sunnewsonline.com/webpages/opinion/editorial/2011/oct/14/editorial-14-10-2011-001.html
- Teck-Chuan, V., Chin, J. and Campbell, A. (2008) *Multinational Research.* New York: Hastings Center.
- Washington, H. (2011) *Deadly Monopolies*: *The Shocking Corporate Takeover of Life Itself--And the Consequences for Your Health and Our Medical Future.* New York: Doubleday.
- Wellcome. (2011) http://genome.wellcome.ac.uk**.**
- Witten, J. (2011) Genomycism: "Deflating The Genomic Bubble" http://www.science20.com/rugbyologist/genomycism_deflating_genomic_bubble-76472 accessed 5/10/2011

Further Reading: Guidelines and standards

- AAP - American Academy of Pediatrics (2001) *Ethical Issues with Genetic Testing in Pediatrics*.
- BMA – British Medical Association (2001) *Consent, Rights and Choices in Health Care for Children and Young People*. London, UK: British Medical Journal.
- CIOMS. (2002) *International Ethical Guidelines for Biomedical Research Involving Human Subjects*
- Clothier Report. (1992) *Report of the Committee on the Ethics of Gene Therapy*. London, UK: Her Majesty's Stationery Office.
- Council of Europe (1997) *Convention on Human Rights and Biomedicine*. http://conventions.coe.int/Treaty/en/Treaties/html/164.htm
- DHHS – Department of Health and Human Sciences. (1991) Additional Protections for Children Involved as Subjects in Research, 56, Fed. Reg. 28,032.
- European College Court of Human Rights. (1997) *The Protection of Human Rights and Dignity of Human Beings with Regard to the Application of Biology and Medicine*.
- European Commission. (2004a) *25 Recommendations on the Ethical, Legal and Social Implications of Genetic Testing*.
- European Commission. (2004b) *Medicines for Human Use (Clinical Trials) Amendment Regulations, i*mplemented in English Law(2006) SI 2006/1928.
- MRC - Medical Research Council. (2004). *Medical Research Involving Children.* London: MRC
- *Nuremberg Code* (1947) http://ohsr.od.nih.gov/guidelines/nuremberg.html
- RCPCH - Royal College of Paediatrics and Child Health (2000). Guidelines for the ethical conduct of medical research involving children. *Archives of Disease in Childhood*, 82:117-182.
- UN - United Nations. (1948) *Universal Declaration of Human Rights*. New York: UN.
- UN - United Nations. (1989) *Convention on the Rights of the Child.* New York: UN.
- UNESCO. (1997) *Universal Declaration on the Human Genome and Human Rights.*
- UNESCO. (2005) *Universal Declaration on Bioethics and Human Rights*.
- US National Commission. (1977) *Research Involving Children: Report `and Recommendations*. Washington, DC: US Government Printing Office.
- WMA – World Medical Association (2008 [1964]) *Declaration of Helsinki*.

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Glossary

Genetics is immensely complicated, with great areas still waiting to be discovered, so this glossary is simply a very basic introduction. Terms are not in alphabetical order but in a sequence of related ideas.

Autosomal genetic conditions*.* In the human body, except for the red blood cells, each of the 100 trillion cells has a nucleus containing the double helix of 46 chromosomes arranged in 23 pairs, one pair from each parent, with numerous genes arranged along each chromosome. The first 22 pairs are autosomal chromosomes,

and the 23rd pair is the sex chromosomes. Autosomal genetic conditions, from genes on the first 22 pairs, are passed on from mothers or fathers to sons and daughters. They include sickle cell anaemia and cystic fibrosis.

The genes for **sex-linked genetic conditions** occur on the 23rd pair of chromosomes, an X and a Y in males, two Xs in females. The conditions include muscular dystrophy, which mainly affects boys. With the blood disorder haemophilia, mothers inherit the trait, but not the full condition. Their sons may inherit the full condition, their daughters may inherit and later pass on the gene. Females are almost always asymptomatic carriers, and can inherit the defective gene from their mother or father, or may have a new mutation. Very rare cases of females with haemophilia have a haemophiliac father and a carrier mother. The extremely rare non-sex-linked haemophilia C can affect either sex.

In a **dominant genetic condition,** one parent carries a gene related to the specific inherited condition, with a 50 percent chance of passing it on to the children. An example is Huntington disease.

In a **recessive genetic condition** both parents, who may be disease free themselves, carry one normal gene and one altered gene. Each child has one chance in four either of inheriting two altered genes and developing the disorder or of inheriting two normal genes, and one chance in two of being a carrier like both of the parents. The conditions include sickle cell anaemia and cystic fibrosis. Parents may not know that they are carriers until they have a child with the condition. However, in areas of Cyprus where thalassemia is common, couples must attend pre-marital counselling and testing for carrier status.

Epigenetics, ‘epi’ meaning ‘as well as’. describes anything other than the actual DNA sequence that influences the development of an organism and heritable traits. It does not involve changes to the underlying DNA sequence, but activates certain genes without altering their structure. Effects can occur across two generations (Russo et al., 1996).

Consent is an informed, voluntary, legally valid choice and decision. Consent may be granted or refused.

Competence to consent may be assumed (in most adults) or assessed (in children and people with learning or mental difficulties). Competence is assessed by status (usually broad age groups, such as adult or baby), by outcome (the assessor agrees with the person’s decision) or by function (the assessor may disagree with the decision but considers the decision making process was logical and valid). Function is the fairest way to assess competence. English law allows that minors aged under 16 (no specified lowest age) can be *Gillick* competent, and able to make legally valid decisions about treatment, although there is less certainty about minor’s rights to consent to research.

With **opt-in** research, People are sent information and asked to contact the researchers if they wish to know more or to take part in the research. A lower ethical

standard is **opt-out**, when people are directly asked to enrol in a project and they have to express refusal if that is their choice.