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Applying bioethical principles for directing investment in precision medicine

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Abstract

The concept of precision medicine aims to tailor treatment based on data unique to the patient. An example is the use of genetic data from malignant tumours to select the most appropriate oncological treatment. The competing interests of utilitarianism and egoism create dilemmas for decisions regarding investment in precision medicine. The need to balance the perceived rights and needs of individuals against those of society as a whole is an on-going challenge in the distribution of limited health service resources. There is need for proper planning, organisation and investment into precision medicine to cope with the consequences of both direct-to-consumer and healthcare-directed genetic testing for genetic counselling, therapeutics and diagnostic networks. Consideration needs to be given to providing adequate time and training to allow for meaningful shared decision-making with patients and there is a strong case in support of a hub-and-spoke model to provide rapid, solid tumour genetic mutational analysis to prevent patients missing out on beneficial treatments.

Keywords

Bioethics and medical ethics, genome mapping and sequencing, resource allocation, healthcare economics, genetic counselling, genetics and genomics

Precision medicine describes the use of biomarker data from companion diagnostics to highlight a subsection of a specific cohort of patients who might respond to a particular treatment.[1] Companion diagnostics can take a number of forms and include testing modalities such as immunohistochemistry and genetic sequencing. Stratified medicine is often used in an oncological setting for patients with late stage malignancies that have a guarded prognosis. Oncological treatments linked to companion diagnostics in this way are novel and expensive. This is an active area of medical research and there are likely to be new drugs provided by the NHS that use companion diagnostics with resulting potential for increased financial burden to the NHS, not only through the cost of drugs, which can run into many thousands of pounds per patient per month, but also through the additional cost of testing large numbers of patients to highlight the subset who may benefit. It is therefore important to consider the ethical principles that underpin investment in precision medicine.

This essay will focus on ethical issues relating to companion diagnostics in cancer patients and consider arguments for and against how to direct investment using opposing consequentialist theories of ethical egoism and utilitarianism.

The first issue in relation to use of companion diagnostics in personalised medicine is who decides whether to test or not. Within the NHS most of these decisions are taken at the multidisciplinary team (MDT) meeting as a collective decision between physicians, nursing staff, oncologist, radiologist and pathologist. These are multifaceted decisions that take into consideration a number of factors such as the histological subtype of cancer, patient performance status, prognosis, social circumstances and patient wishes. This process excludes the patient themselves in a way that is

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considered counter to patient autonomy, a key bioethical principle underpinning patient care.[2] There is an argument for including patient advocates and or the patients themselves in MDT meeting to allow them to contribute to decision-making.[3] Shared decision-making is an important component of the doctor–patient relationship and such collaboration would be in keeping with GMC guidelines of good practice.[2,4,5] However, shared decision-making, outside of an MDT setting, is a complex process and said to be rarely accomplished in real-life clinical practice.[6] Part of the reason for this may be due to strict research methods and criteria that underestimate when shared decision-making is actually taking place during consultation.[7] There is also a perception that fully informed shared decision-making takes too much time[8] and that evidence for the benefit of that extra time investment may not be readily apparent to the clinician during a busy clinic.[7]

Patient autonomy is a key bioethical principle in medical practice[4,9] and describes patients having the ability to freely choose and determine their fate with independence.[10] The freedom to make a choice based purely on ones' own self-interest would align with Smith's[11] theory that pursuit of self-interest ultimately results in good for all society as if by 'an invisible guiding hand' and this forms the basis for the consequentialist theory of ethical egoism. Patient autonomy requires that patients are in possession of the full facts of their case presented in a clear and understandable way without biased interference by doctors or family members.[12] Patient autonomy is being respected when patients are offered treatment by an oncologist on the basis of full and accurate information. This includes accepting a competent adult patient may refuse treatment regardless of whether it appears sensible to the healthcare professional. This is embodied by Mills'[13] summary of autonomy thus, 'Over himself, over his body, and mind, the individual is sovereign'. There is no evidence in the medical literature around how many patients decline precision medicine in the UK. In the US, however, there is evidence that patients who pay for their own treatment have a reduced compliance rate due to the high costs.[14] Provision of health services on the basis of need rather than the ability to pay, as happens in the NHS, means that this situation is unlikely to occur in the UK. Provision of full and accurate information during consultation needs to be provided in the context of patient power to be sure that decision-making is truly shared.[15] Patients having real influence on medical decision-making represent an example of procedural justice.

A further issue around precision medicine concerns who decides what to invest in and how. In the UK these decisions are taken by the state, who direct health policy, and by executives who manage the NHS. The NHS is generally guided by fundamental principles of utilitarianism and described by Mill[16] as the best use of resources for the greatest good within the population.[17,18] Whilst on the surface, precision medicine using companion diagnostics appears to fit with this principle very well i.e. using expensive drugs only in those patients who are likely to benefit. However, the high cost of these medications may tip the balance in favour of non-investment in this technology in favour of cheaper preventative measures.[19]

Prescribing expensive novel oncotherapeutic agents linked to companion diagnostics will reduce therapy costs compared with providing the treatment to all patients and there is a wealth of evidence demonstrating that such agents are effective. Recent scientific developments in the molecular events of lung cancer pathogenesis mean that it is often cited as a 'role model' for precision medicine.[20] A good example is the use of tyrosine kinase inhibitors (TKIs) in the treatment of advanced adenocarcinoma of the lung.[21–25]

These agents can give overall survival benefits of 13 months and between 14 and 17 months, respectively, when used in the setting of lung cancer.[23,26] It is difficult to argue against the deontological principle of a right to life[27] and every patient with a terminal illness is likely to feel strong leanings towards egoism when considering their own mortality. However, from a utilitarian perspective it may be of more benefit to more people to redirect the large sums of money involved in funding these novel oncotherapies towards early diagnosis and/or disease prevention to potentially benefit a larger number of patients.[19] Many of these oncological drugs have been approved for use in the NHS by the National Institute of Health and Care Excellence. It is evident that emotive arguments from the few can influence decision-making by the state through the media and court action as was the case with Herceptin.[28] The government and the media were criticised by the medical profession at the time for not being able to step back from individual terminal cancer cases and make resourcing decisions for the benefit of the many.[19]

Investment would be required to ensure that precision medicine services are of sufficient quality to be reliable and this would include staffing, equipment and processes that comply with clinical standards. There is a conflict that arises when balancing quality, costs and timeliness in the diagnosis of lung cancer.[29] Greater efficiencies are said to occur with larger batches of tests and centralisation of services in large, single centres.[30–32] There is a counter argument to this approach when one considers slow turnaround times resulting from batching of diagnostic tests.[33] Again, using the example of lung adenocarcinoma, it is now

possible to perform EGFR receptor mutational analysis locally using a fully automated, clinically validated real-time PCR platform that yields results in under 3 h.[34] A point-of-care testing service would require investment in technology and staff but has clear benefits for patients who may deteriorate in the 2–3 week wait for results from a centralised laboratories using next generation sequencing (NGS) technologies. The ToGA study[35] showed that 25% of patients with gastric or gastro-oesophageal junction adenocarcinoma were denied treatment with Herceptin because they became too unwell for treatment whilst waiting for a HER-2 immunohistochemistry report which, during that study, took around two weeks to provide. Being able to offer TKI therapy also relies upon patients being well enough to receive the treatment; they need to be performance status 0 or 1.[36,37] If the findings of the ToGA study are reflected in patients with disseminated lung adenocarcinoma, then there will be a significant number denied therapy that offers significant progression-free survival advantages. The number of patients who are denied such treatment is not provided in the medical literature yet and this is an area of research need for the future. This is, therefore, evidence to support investment in a hub-and-spoke model of solid tumour genetic analysis where a central hub provides NGS back-up for localised point-of-care, rapid PCR assays that provide actionable genetic mutation results for oncologists and patients on ethical grounds of a patients' right to life and the pursuit of both beneficence and non-maleficence.[9,12,18]

It is possible that patients may perceive discrimination when looking at the observable characteristics of individuals receiving TKI therapy for adenocarcinoma of the lung. This is because the somatic genetic mutation within the tumour occurs with greater frequency in young, Asian females who have never smoked.[38] Differences in patient smoking status may be misconstrued and perceived as bias by a treating organisation on the basis of what is perceived by society to be a harmful lifestyle for which taxpayers bear the cost.[39] It may be useful to investors in this area to consider the possibility for misconception by patients. This risk may be mitigated against by the production of detailed patient information leaflets freely available in the oncology outpatient waiting room.

There is evidence of increased use of direct-to-consumer (DTC) genomic testing by patients and this also applies to sequencing of solid tumours.[40] The reasons for this are unclear but cancer patients often use support groups both online and in person for emotional and social support. Whilst these networks are likely to be beneficial in psychosocial terms, they may highlight differences in oncological treatment practices across the country.[32] Autonomy, dignity and integrity and mortal desperation all drive the need to explore treatment options, including untested experimental ones. This is an example of self-interest pursuit that underpins ethical egoism and drives, in part, the DTC genetic testing market. This is at odds with utilitarian principles that form the basis of workings in the NHS. Reports generated by DTC companies have the potential to create conflict within the doctor–patient relationship where tumour molecular profiling highlights somatic genetic mutations that also have implications for the germline and hence family members.[41] Healthcare professionals may encounter difficult ethical situations where maintaining patient confidentiality in the face of preventing harm to uninformed relatives becomes difficult in situations where patients refuse to discuss their medical issues with their family.[41,42]

Meadowcroft argues that governments have a responsibility to restrict market forces that exploit vulnerable patients who pay for tumour genomic information in the context of a terminal cancer diagnosis.[35] In addition, there are problems with knowing the relevance and risk that identification of variation by genomic analysis raises and the general consensus amongst medical professional is that patients should be discouraged from using these services until such time the full implication of their findings is known and evidence based.[43] The counter argument is that restricting DTC genetic testing undermines respect for patient autonomy.[44]

Patients are also using DTC testing for predicting future cancer risk.[45] 'Expert advice' received in the accompanying DTC genetic reports can be inaccurate and misleading[43] and there is also evidence that people do not necessarily change their risk behaviours in accordance with the information they receive.[46] These are usually healthy people who are receiving information about risk associated with single nucleotide variation linked with multifactorial risk of cancers such as colorectal cancer.[47] Again, full understanding of how a person's genes interact with the environment to determine precise risk of developing such cancer is not fully understood and the provision of DTC genomic testing is not fully regulated.[44,48] Some of these arguments are used to support the call for increased regulation of the DTC genetic testing industry.[43,49]

What may not be fully considered before taking up DTC testing in a setting of malignancy is the potential for identification of mutations that carry implications for family members through the germline.[50] There are many genes that have been shown to have implications for germline inheritance that may be identified during testing for somatic mutations in cancers,[50] and the best characterised of these is BRCA1/2 associated breast and ovarian cancer syndrome.[51–53] As well as dealing with the uncertainty around infrequently encountered

genetic variants and knowing how they translate into phenotype, there is also the need to provide genetic counselling before testing so that patients can make an informed choice, not only for themselves but also for family members.[43,54] This requirement is based on the principle of patient autonomy and informed consent. Patients (and their family members) can only make a choice based upon adequate information and influence before they proceed.[15,55,56] Testing and referral to genetic counselling after the event of revealing a genetic variant creates difficulties for professionals and their relationships with patients in an outpatient clinic by undermining this principle.[57] Genetic testing without prior patient consent denies patients an opportunity not to know the findings.[55] There is a need for investors in precision medicine to ensure there are enough genetic counsellors and clinic time to cope with the inevitable increased demand that precision medicine and genetic testing of malignant tumours will bring.[49,56]

In conclusion, the competing interests of utilitarianism and egoism create dilemmas for decisions regarding investment in precision medicine. The need to balance the perceived rights and needs of individuals against those of society as a whole is an on-going challenge in the distribution of limited health service resources. There is need for proper planning, organisation and investment into precision medicine to cope with the consequences of both DTC and healthcare-directed genetic testing for genetic counselling, therapeutics and diagnostic networks. Consideration needs to be given to providing adequate time and training to allow for meaningful shared decision-making with patients and there is a strong case in support of a hub-spoke model to provide rapid, solid tumour genetic mutational analysis to prevent patients missing out on beneficial treatments.

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