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Article

The "Molecularly Unstratified" Patient: A Focus for Moral, Psycho-Social and Societal Research

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Abstract
The biomedical paradigm of personalised precision medicine – identification of specific molecular targets for treatment of an individual patient – offers great potential for treatment of many diseases including cancer. This article provides a critical analysis of the promise, the hype, and the pitfalls attending this approach. In particular, we focus on "molecularly unstratified" patients – those who, for various reasons, are not eligible for a targeted therapy. For these patients, hope-laden therapeutic options are closed down, leaving them left out, and left behind, bobbing untidily about in the wake of technological and scientific "advance." This process creates a distinction between groups of patients on the basis of biomarkers and challenges our ability to provide equitable access to care for all patients. In broadening our consideration of these patients to include the research ecosystem that shapes their experience, we hypothesise that the combination of immense promise with significant complexity creates particular individual and organisational challenges for researchers. The novelty and complexity of their research consumes high levels of resource, possibly in parallel with undervaluing

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other "low hanging fruit," and may be challenging current regulatory thinking. We outline future research to consider the societal, psycho-social and moral issues relating to "molecularly unstratified" patients, and the impact of the drive towards personalisation on the research, funding, and regulatory ecosystem.

Introduction

The zeitgeist of contemporary medicine has been built on the promise of personalised, precision medicine (PPM) that utilises the biomedical revolution's newest tools and targeted treatments. The European Alliance for Personalised Medicine Congress articulates what is widely taken to be the logical, ethical response to this promise by describing "Personalising your health" as "A global imperative!" The future hope – "personalisation of your health will happen" – provides the logic of a present command – "personalise everyone's health, everywhere!" Personalised medicine's basic ethical commitment thus follows the structure of promissory enterprises. This is a structure with which humanity is very familiar, especially in religions in which future hope or expectation gives the rationale for current activity.

Nowhere is this modern biomedical paradigm more acutely promised and to some extent realised than in cancer care. Especially in high-income countries, the public discourse is fed, daily, with the fuel of this promise; new precision medicines and biomarkers, and new discoveries in the fundamental aspects of molecular biology. Our concern here and in ongoing research is to examine the influence of this zeitgeist on the research ecosystem which surrounds PPM. In particular, we focus initially on the experience of "molecularly unstratified" patients in clinical trials: the patients who, for whatever reasons, do not fit or are not offered a novel treatment.

Our previous research has critically analysed the promise, the hype, and the pitfalls surrounding PPM and made recommendations regarding policies and imperatives. A summary of that research follows, setting the stage for examining the experience of molecularly unstratified patients and the ecosystem of which they are members [1].

First, recalling the complexly interdependent commercial, academic, and state actors involved in PPM, we emphasise critical awareness and realism "about the sources of innovation, other-regard and selfishness." These reflective attitudes are vital to fostering "a research environment which serves the public interest" and identifying temptations that tend towards neglect of that interest. In our view, such "temptations to neglect largescale public benefit may overwhelm even the best motivated private actors." From a patient and clinician perspective, we analysed "the clinician's mediating role amidst the factors which shape patient experience" with a view to "ensuring that population-level public health approaches are not forgotten in the search for ever more precise approaches to prevention" [1– 7].

Second, we explored the patient and public experience of PPM. We suggested that while "stratified medicine offers a newly precise kind of humanising health care through societal solidarity with the riskiest…stratification may also mean that patients who do not fit into the sought after molecular subtypes experience accentuated suffering and disappointment." Accordingly, further research should explore "the risks to care of persons attendant on a focus on biomedical cure, construed at a molecular level [and] whether it is possible and beneficial to stratify on the basis of psychological factors as well as biological ones" [1].

Further, we warn against the assumption that engagement with stratified medicine will be optimal. Non-adherence to pharmaceutical treatments is extensive, with WHO estimating

that half of prescribed medicines are not taken as advised [8]. We therefore need a better understanding of how stratified medicine will be perceived by patients and the public. This implies research into "how healthcare professionals might be better trained to pay attention to the interaction of the communication of genomic information with the values and beliefs of patients, especially as regards their future happiness; and how the entire enterprise of personalised medicine might develop a wiser compassion for the patients as persons whom they seek to serve" [1, 3–5].

As regards compassion and over against the idea that we can "know ourselves" cheaply through more cost-effective genome profiling, we argued that PPM needs to collaborate closely with humanities and social sciences. For example, many patients' cultural forms of self-knowledge and understandings of the future are bound up in complex ways with questions of theology and religion [3, 9].

Third, we analysed legal, philosophical and regulatory questions regarding data use, sharing and ownership. A controversial proposal made was that ownership of data "might more plausibly lie with health professionals than patients" and that "in a socialised medicine system, such as the NHS, such professionals are agents of the state, and ownership would lie with the commons rather than any individual. This means that common rather than private ownership of genomic information may be more appropriate." The plausibility of this claim is given further weight by the notion that data on an individual only has value and meaning in the context of other information that is part of the commons [10].

Such data-related issues have significant impact on the research ecosystem in which researchers, trial designers, managers, clinicians, and funders operate. Better systems of data sharing and conceptions of data ownership seem essential to serving not just the best interests of a sub-group identified as appropriate for a novel treatment but all patients involved in clinical trials, including, in particular, molecularly unstratified patients [1, 10–12].

Fourth, we considered precisely what national and global imperatives should govern issues of resource allocation and equity. We observed how "the threats of inequity and poor value healthcare for those least able to stand up for themselves attend the 'advance' of personalised medicine. This raises the question of what responsibility medical researchers actually have for national and global inequity when control typically lies in the hands of governments, commissioners, and payers. To put matters starkly, is personalised medicine potentially a Trojan horse for a neoliberal research agenda which will only be available for the rich in many countries? Such a development might put at risk the socio-political ethos of risk-pooling which underpins the vision of solidarity in healthcare" [2, 4, 13, 14].

Interrogating the value and vested interests inherent in PPM processes focusses attention not just on those who *do* fit the novel treatment but on the (often) very many who *do not*. We believe that making molecularly unstratified patients far more central to trial design and policy will not only drive forward research to benefit such patients but will generate critical questions and focused solutions to the issues of equity, solidarity, value and interest which lie within PPM.

We concluded that paying "attention to (molecularly unstratified) patients is a next logical step in scrutinising the distinction between hype and reality" and to identifying key ethical imperatives with respect to the personalisation of health. Accordingly, we are now investigating the following question: "what moral, psycho-social, and societal issues are important in relation to such patients and how might they be best addressed?" As discussed below, to answer this question, the wider research ecosystem of which molecularly unstratified patients are members must also be considered.

The "Molecularly Unstratified" Patient

Within PPM, the overwhelming focus is on drug discovery and development linked to companion diagnostics which identify the patient group in which benefit is predicted. In order to obtain evidence of clinical benefit, pharmaceutical companies have to pre-screen patients to find those positive for the biomarker, and then seek to enrol those biomarker-positive patients in those trials. In a widely quoted example evaluating an FGFR-targeted therapy in gastric cancer, AstraZeneca have had to screen 70 patients to find 1 eligible patient for the trial. In an effort to be more inclusive, academic investigators have established "umbrella" trials in which a diagnostic platform screens patients' samples for a number of biomarkers and allocates the patients into the relevant biomarker-defined cohort for trial entry. In this context, there is an expectation raised of being able to access a novel therapy which is personalised – designed for you. The inevitable consequence, however, is that for some or indeed the majority of patients, the biomarker is not present or detected in the patients' tumour or other biosample. They are therefore excluded and become "molecularly unstratified."

The clinical significance of being "molecularly unstratified" is that hope-laden therapeutic options are closed down and allocation to non-targeted or standard therapeutic treatments, or supportive care becomes the only path. Those without the distinction of molecular specificity are excluded from eligibility to many targeted therapy trials. Consider, by way of an example which seeks to address this tendency, the 100 patients in the FOCUS4-N trial, who would have been excluded, had there not been an arm of the trial designed specifically for this "unstratified" group [15, 16].

While becoming unstratified may be due in some instances to technical failure of the assays or inadequate tumour content in the biopsy, or lack of access to a particular agent, it can, more importantly, also be due to a lack of knowledge of how to target the tumour's molecular characteristics in these specific patients. This lack of knowledge can then make this group a focus for further research.

However, this is increasingly challenging since it is significantly easier to identify therapeutic approaches within biomarker-defined cohorts where a number of treatments have been developed, compared to the challenges of, for instance, *RAS* mutant or *MYC* amplified tumours, where no therapeutic approach has been established. Therefore, for the unclassified/unstratified patient, what remains is a speculative search for genetic or other disease drivers, a process much further back in the developmental pathway when compared to current therapeutic intervention, implying many years or decades of waiting before a therapeutic could emerge. Precision is being aimed at and yet not (or not yet) being delivered upon for these patients.

But what moral, societal, psychosocial issues attend the molecularly unstratified experience? What are the imperatives for this group of patients and what impact might answering this question have for policy and practice? The concerns underlying these questions are the possible de-prioritisation of certain avenues of research, the extent to which people are being left out and left behind and the extent to which the research which might serve them is being downgraded and underfunded.

The deflation of hope among the unstratified, the difficulties of effective communication and the challenges of identifying next treatment steps may have the side-effect of a psychosocial distinction between unstratified persons and those "lucky" enough to be stratified in some way. Such a distinction could become a widespread, quite self-conscious experience in society as the expectation of personalised precision, powered by a heady mix of clinical and scientific promise and hype and the global imperatives that apparently follow, seems likely to become increasingly part of public and patient experiences. If researchers, trial designers,

managers, clinicians, and funders fail to address this experience of being a "molecularly unstratified" person/patient as an issue requiring moral analysis and research focus, a dilution or at least pronounced heterogeneity in the public's welcome of stratified/personalised approaches may follow.

These concerns about the impact of the experience of "molecularly unstratified" patients should be seen against the backdrop of patients' general engagement with stratified treatments, which it is often assumed will be optimal. There are few studies of patient perceptions of PPM, but the few that have been published suggest that this assumption may be misguided [17]. Research is needed to examine patient and public perceptions of PPM to understand how we might support informed decisions and optimal engagement [18].

To specify, clarify, and address these issues, our research will draw on social scientific approaches and humanities disciplines such as the psychology of illness and treatment representations and philosophical and theological ethics. The aim is to consider moral questions which surround the care of patients for whom the particular molecular nature of their cancer or other condition becomes the occasion of both feeling and being left out, and left behind, bobbing untidily about in the wake of technological and scientific "advance." To the extent that the zeitgeist of PPM may suffer from a technological and pharmaceutical quasi-messianism, patients' suffering may become aggravated by the unrealised hype of such a "tech-messianic" promissory culture.

The Ethos of Stratified Medicine: Causes for Concern?

Consideration of the experience of molecularly unstratified patients and the research and clinical imperatives appropriate to serve their best interests constitute the entry point and initial focus for this project. But to enter the research ecosystem at this juncture and in this way prompts further investigation of the ethos of stratified medicine as a whole in which researchers, trial designers, trial managers, clinicians, funders, government, and commercial actors are heavily invested, vocationally, financially, and in terms of reputation.

While it was engagement with patient experience which has stimulated investigation of what is going on in this wider ecosystem, it is also reasonable to suppose that patients could benefit from understanding the challenges and pressures that those professionally engaged in conducting trials are facing. Inasmuch as PPM is a joint endeavour, some degree of mutual, compassionate understanding by each part of every other part would seem imperative to the flourishing of the whole.

Concerns

It is our working hypothesis that significant researcher and clinician distress and burnout accompany PPM research. Analysing the effects of the "imperative" of personalisation on the whole research, funding and regulatory ecosystem seems itself an imperative for understanding why this happens wherever it does happen. There are 2 reasons for thinking this an important area for research.

First, the experience of hype-deflation and demoralisation seems likely to accompany the immense promise *and* vast challenges of attaining a precision which will serve patients. On one level, this experience is just a normal part of scientific enquiry. But on another level, the dual forces of the attractive idea that precision might provide complete cure and the needs of the subpopulations crying out for such aid create certain possible threats, specific to PPM researchers. What needs analysis is whether the system of evaluating the conditions of success in PPM research itself engenders certain ethos problems. Other kinds of medical research are quite self-consciously about steady progression and not so contingent on a

binary cure/non-cure, yes/no outcome. But the value of PPM research seems contingent on making the longshot (or moonshot), the discovery of the "holy grail" cure, the firing of the magic bullet against disease. This ethos seems likely to increase what are perhaps normal experiences of disappointment and demoralisation to a significant degree.

Second, there is a risk that the very viability of the work PPM researchers undertake is under threat by the environment in which it is being conducted. Stratified trials are inherently large and complex undertakings, with a high degree of novelty. Perseverance in the compassion which may be assumed to be a basic attitude among those conducting trials can become swamped and shipwrecked by the significant operational challenges that we have observed, so that lives and careers are also left bobbing about behind the cresting wave receding into the distance. The related high levels of organisational debilitation and individual stress and burnout, where they exist, would seem likely ultimately to impact trials' capability to deliver high-quality results.

It is therefore a further hypothesis that the quality of the regulatory environment will be determinative of the extent of debilitation, stress and burnout [19]. A key focus for understanding the ethos of the work environment across trials would thus be principles operative on a regulatory level. Whereas the "precautionary principle" has predominated in research in Europe in recent years, there is a new emphasis on an "innovation principle" [20]. While innovation is often conceived over against precaution, it may also be seen not as precaution's rival but rather as its necessary complement [21]. The extent to which this "innovation principle," where adopted, is shaping the ethos of the PPM research environment for the better or worse is a proper focus for research. A further, particularly acute angle for investigation would be the extent to which this will vary between the UK and the continuing 27 members of the EU following the UK's exit from the EU. Ethnographic and moral analysis would be necessary to investigate this specific dimension of the research over time.

A final concern is the opportunity cost which may be associated with the huge amount of highly skilled energy being expended on pursuing molecularly targeted therapies, thereby creating a culture of undervaluing simpler approaches, which may come to be perceived as old-fashioned. Is the current ethos of the research ecosystem operating in such a way as to demotivate the picking of any remaining "low-hanging fruit" which might bring real benefit to patients, including but not limited to molecularly unstratified patients?

While colorectal cancer has been the initial focus in this study, our approach will be to work across a variety of settings and trials (e.g., other UK Medical Research Council stratified medicine consortia) in order to identify the extent of diversity or similarity in the approaches taken and issues raised.

Methods and Approaches

Across these concerns, there is a need for ethnographic description and moral analysis of what shapes the ethos and direction of PPM research ecosystems. In what way and how is vision and research energy attracted and organised or, to put it more provocatively, corralled and captured? To be more precise, how does this show up in the orientation of funders and commercial pharmaceutical actors towards research in certain metastatic diseases especially those whose early detection might be possible, given sufficient resources (e.g., how to detect those at risk of pancreatic cancer at year 1 or even year 10 rather than year 16 in its evolution)?

Methodologically, the success of this project will be the coordination and interpenetration of 3 kinds of research: qualitative and ethnographic description of the research ecosystem, especially the experience of molecularly unstratified patients and researchers; systematic cultural-ethical analysis of both the questions which shape such qualitative work and the conclusions of such work once completed, drawing on the disciplines of philosophy,

theology, psychology and social sciences; and molecular-level research carried out by clinicians and scientists, in partnership with patients, which aims to identify the longed-for novel and effective treatments.

Expected Outcomes

The project's expected outcomes are twofold. First, recommendations would follow for how to refocus on unstratified patients both culturally with respect to rebalancing the discourse and rhetoric around PPM and, on a more granular level, with respect to the thinking behind trial design.

Second, with respect to the wider researcher ecosystem, recommendations for regulators and funders would follow concerning how trials can be better shaped to support those conducting them in the face of what may be a widespread, debilitating, and corrosive experience of research. Organisation of trials would be influenced by the moral, psycho-social, and societal factors operative within the experience of molecularly unstratified patients and within the wider research, funding, and regulatory ecosystem.

In summary, the imperatives which emerge from this research will very likely cut across the mainstream atmosphere of PPM by paying attention to neglected Achilles' heels which can hamstring the enterprise as a whole, including the reputational risk to PPM and the demoralisation risk among staff. Neglect of these matters may result in PPM being less compassionate to those at risk of being left behind, more debilitating to those conducting the trials, and less plausible to the governments and populations on whose good will and financial support the enterprise to some extent rests.

Research Trajectory

In order to pursue this work, we intend to proceed as follows.

1. First, we will examine the process of becoming "unstratified" in one particular trial, through post hoc analysis of choices made by clinicians and patients regarding participation in the trial.
2. Second, we will conduct a limited qualitative study of those conducting specific trials, to suggest causes and factors behind hypothesised burnout, debilitation, and distress.
3. Third, these initial pieces of analysis will inform a future funding bid for a wide-ranging, multi-setting, multi-trial study of the research ecosystems of which molecularly unstratified patients are members. This will entail an ethnographically, economically, and ethically informed analysis of the state of play in precision, personalised medicine. Deploying psychological, sociological, philosophical, and theological modes of analysis, this work will examine culturally engrained expectations, assumptions, and narratives within PPM in order to identify and address moral, psycho-social, and societal issues.

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