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Pharmacogenomic Inequalities: Strategies for Justice in Biomedical Research and Healthcare

PHARMACOGENOMIC INEQUALITIES: STRATEGIES FOR JUSTICE IN BIOMEDICAL RESEARCH AND HEALTHCARE

– Giovanni De Grandis –

Abstract. The paper discusses the possibility that the benefits of pharmacogenomics will not be distributed equally and will create orphan populations. I argue that since these inequalities are not substantially different from those produced by 'traditional' drugs and are not generated with the intention to discriminate, their production needs not be unethical. Still, the final result is going against deep-seated moral feelings and intuitions, as well as broadly accepted principles of just distribution of health outcomes and healthcare. I thus propose two provisos that would prevent the most offensive outcomes and moderate the scope of the produced inequalities. The first proviso rejects pharmacogenomics innovations that worsen existing group inequalities and aggravate the disadvantage of communities with a history of discrimination. The second proviso requires that there is a strategy in place to even out as much as possible the distribution of benefits in the future and that a system of compensations (in terms of healthcare services) is in place for pharmacogenomic orphans. Given that only one moral problem generated by pharmacogenomics has been tackled, the list of provisos might be expanded when other issues are considered.

Keywords: pharmacogenomics, justice, health inequalities, healthcare ethics, pharmaceutical research and development.

Introduction

Questions of justice in health achievements and in access to healthcare have received considerable attention in the last 3–4 decades as well as having stimulated the birth of bioethics.[1] Two main approaches to justice in health can be identified. There are studies that on the basis of social scientific empirical research point out that socioeconomic differences lead to different levels of longevity and health (for instance, intended as disease- and disability-free life years). Often these studies combine the empirical evidence with an ethical or political critique of this state of affairs, based on the intuition that current levels of health inequalities are unjust

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[1] Possibly the most emblematic early example was the establishment in 1960 of the Admission and Policy Committee by the Seattle Artificial Kidney Center to decide which patients should be given access to the haemodialysis machines given that the demand far exceeded the Center's capacity (Jonsen [2000] p. 104–106).

and need to be reduced.[2] The other approach instead focuses on the allocation of scarce healthcare resources and attempts to find justifiable ways to apportion them, given that it is not possible to meet every health need. This literature typically relies on philosophical (normative) approaches to distributive justice.[3] Pharmacogenomics may bring with it challenges from both points of view. There are concerns that because of the existing structure of incentives for pharmaceutical R&D, pharmacogenomic drugs will meet the needs of those social groups that already enjoy economic and health advantage, while potentially taking away resources from programmes that would benefit the worse off groups. But pharmacogenomics raises important questions also for priority setting in the allocation of healthcare resources. Indeed, the paper shows that pharmacogenomics forces us not to limit our ethical concerns to the distribution of healthcare resources, but to consider also the production of new treatments and the reasons behind production choices. This shift in perspective challenges in particular the interpretations of health needs in terms of the capacity to benefit, for the moral case for innovation rests precisely on the attempt to help those who, under current medical knowledge and technology, enjoy very little capacity to benefit.

The first goal of the paper is thus to show that pharmacogenomics forces us to think of the role of biomedical innovation in health and, in so doing, broadens the scope of health-related distributive justice to include research and innovation policies. This may require the development of new ethical and economic frameworks—a task that is not attempted here. The other and more substantive goal of the paper is to begin to sketch the conditions under which distributive inequalities generated by pharmacogenomics are acceptable.

Most theories of health justice developed for democratic regimes insist on some sort of duty to provide basic healthcare (where the service baseline is relative to economic development and democratic choices around the allocation of resources) and equality of access as a basic requisite of justice in healthcare. Equality of access can mean several things, but a fairly basic and fundamental understanding is that differences in economic status, gender, race, religion, health status, age etc. should not affect the entitlement to receive whatever level of care is compatible with an affordable and sustainable universal healthcare system. A telling example of the widespread acceptance of the idea that the level of healthcare needs to be commensurate to the resources of a society can be found in *General Comment*

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[2] E.g. Black et al. [1980]; Shaw et al. [1999]; Wilkinson, Marmot [2003]; Bartley [2003]; Mackenbach [2006].

[3] E.g. Daniels [1985, 2007]; Anand, Peter, Sen [2005]; Powers, Faden [2008]; Fleck [2007].

14: The Right to the Highest Attainable Level of Health by the United Nations' Committee on Economic, Social and Cultural Rights.[4] This requirement of course is compatible with people getting better or further care at their own expenses; so rather than as egalitarian, it is more accurately described as non-discriminatory access to basic care. To put it another way, the basic requirement demands that a system of healthcare is in place in order to offer treatment on a non-discriminatory basis, but within limits set by budgetary constraints. All are entitled to affordable and sustainable care, but not to every state-of-the-art treatment.

Non-discrimination is thus at the heart of the most basic understanding of just allocation of resources for health. Now this basic principle is challenged by the emerging 'omics' disciplines and technologies. The vision of a genomic-powered personalised medicine aims to leave behind one-size-fits-all medicine and become able to tailor diagnosis and treatment on the molecular features of patients (or, more plausibly, of subgroups of patients). This vision has so far advanced more slowly than it was announced, but one field of genomic medicine that has attracted conspicuous investment and that has managed to find its way into clinical practice, at least in some areas of medicine, is pharmacogenomics.[5]

Pharmacogenomics aims at understanding how variations in the genome or in the expression of some genes affect disease pathways, as well as the action and the metabolism of drugs. This promises advances at different levels: 1) avoiding Adverse Drug Reactions and allowing better dosage of drugs to achieve maximum effectiveness and minimize side effects and wasting; 2) rescuing drugs that had been withdrawn—because of severe side effects in some patients—thanks to companion tests that can predict who is at risk of suffering such side effects; 3) identifying new drug targets that can steer drug development; 4) making trials more targeted and hence faster and cheaper.

We can now see that discrimination is a concept that has both a negative and a positive connotation. It is negative in the ethical and political domain, where it is associated with denying equal treatment to some groups because of prejudice or partiality, oppression or hatred. It is positive from a cognitive or epistemic point of view because it indicates the ability to perceive differences that are relevant to fully informed action or judgment. Discrimination in this context is the ability to perceive differences that make a difference and hence not to lump together what needs to be considered in light of its distinctive properties. This may also have an ethical dimension if one—following Aristotle (*Nichomachean Ethics*,

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[4] UN CESCR [2000].

[5] Squassina et al. [2010]; Slaughter [2012]; Johnson [2013]; Evans, Khoury [2013].

Book V.3) and a time-honoured tradition—believes that those who are equal should be treated as equals and those who are unequal should be treated according to their differences, then better discrimination of relevant differences prevents from treating the unequal as if they were equal.

Now the disturbing fact is that the ability to stratify patients on the basis of their genomic profiles can be discriminatory in the positive epistemic sense, but perhaps also in the negative ethical sense. This could happen when analyses of genomic variations are associated with different causal pathways of disease, so that genomically defined subgroups of patients have different disease mechanisms.[6] It is this coupling of a disease mechanism with a genomically specified subgroup that opens the door to fears of discrimination. The disease mechanisms once revealed represent very well specified targets for drug discovery, but which causal mechanism is worth to become the target of drug discovery may depend on the size and some other characteristic of the group manifesting that disease mechanism. To put it crudely: if one disease mechanism is found in a subgroup of patients that broadly coincide with a small and economically deprived ethnic minority, while another mechanism is typical of a much larger and affluent group, it is not difficult to see that the sound business choice is to do research on the latter mechanism/group. The aim of this paper is to discuss whether genomic stratification of patients and disease causal pathways are ethically acceptable. In doing so, the paper also indicates that there is a need to pay more attention to choices taking place in the domain of biomedical research and development (henceforth R&D) because they can have important impact on fairness and equality in healthcare and health achievements. The R&D determinants of health deserve more attention.

It is worth stressing that this paper addresses only <u>one</u> ethical problem generated by pharmacogenomics. Many others, equally important, have been pointed out.[7] So the paper does not aim at offering a comprehensive coverage of the ethical aspects of pharmacogenomics, but rather it discusses at some length only the issue of the unequal distribution of the benefits of pharmacogenomics.

A process analysis of pharmacogenomic stratification

A main point of pharmacogenomics is to provide new and more accurate molecular targets for drug discovery. Genomics in this respect is only one mani-

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[6] It is important to keep in mind that, as Smart et al. ([2004] p. 325) have pointed out, disease stratification and patients stratification do not always correspond (e.g. patients stratification on the basis of drug metabolism does not reflect differences in disease pathways).

[7] See for instance Rothstein, Epps [2001]; Issa [2002]; Buchanan et al. [2002]; Robertson et al. [2002]; Williams-Jones, Corrigan [2003]; Webster et al. [2004]; Smart et al. [2004]; Peterson-Iyer [2008].

festation among others of the new possibilities opened up by molecular biology. Observing and understanding what goes on at the molecular level in patients not only enables a much more fine-grained understanding of the pathological processes, but often reveals that what was considered one disease on the basis of symptomatic descriptions or of a pathological analysis at a larger scale may be divided (stratified) into many more disease types. Indeed new taxonomies of diseases have often been heralded as one of the expected results of the development of what has been variously called genomic, molecular, precision, stratified or personalised medicine[8]. The vision of this stratification of medicine is inspired by attractive medical goals, for it would 1) enable more accurate diagnoses, 2) promote the search for better therapies, 3) reduce the use of harmful and useless drugs, and as a consequence 4) reduce wasteful use of pharmaceuticals and hence contain costs for healthcare systems. How realistic and achievable these goals are is, of course, another question.[9] Since this stratification is not creating groups with different ethical standing, but aims at reflecting biological differences in order to provide more appropriate treatment to each group, it is not in itself ethically objectionable. Notice that here I am simply saying that the scientific reasons for attempting the stratification are not ethically questionable. From the point of view of social policy it is still questionable whether it is wise and fair to invest money and hope in such an enterprise,[10] and whether the scientific expectations are all well-grounded.[11] The very limited claim that I am making here is that researchers pursuing a research project that develops a genomic (or some other molecular-based) stratification of patients or diseases are not doing anything ethically objectionable (they may be doing something wrong in other ways, for instance if they inflate the possible benefits in order to get funds, or if they are driven by the desire of pursuing a race-based medicine).[12]

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[8] On the need for new disease taxonomies see NRC [2011]; on the variety of names see Pokorska-Bocci et al. [2014]; De Grandis, Halgunset [2016].

[9] The need not to take all the claims of pharmacogenomics enthusiasts at face value is stressed by Williams-Jones, Corrigan [2003]. There is a substantial body of research on Personalised Medicine (of which pharmacogenomics is an important part) as *promissory science* (for an overview see Tutton [2012]). The claim that pharmacogenomics will lead to savings for healthcare systems in particular has been questioned since very early (e.g. Rothstein, Epps [2001]) and very often (for some recent examples see: Annas, Elias [2015] p. 32; Joyner, Paneth [2015] p. 1000; Gronowicz [2016] p. 167).

[10] For instance, Bayer, Galea ([2015] p. 501) claim that "the challenge we face to improve population health does not involve the frontiers of science and molecular biology."

[11] See for instance Prasad [2016].

[12] There is a kind of paradox in the relation between pharmacogenomics and race: in principle it could deal race, as a medical concept, a final blow by providing a much more accurate molecular

Turning the vision of pharmacogenomics into a reality is mostly the task of pharmaceutical and diagnostic industry. Public support and funding of research are obviously very important, as it is to create the appropriate regulatory infrastructure and involvement of the healthcare system.[13] Yet, the major role is that played by biotech, pharmaceutical and diagnostic industries. This is both in keeping with a tradition that has seen private firms playing the leading role in the final stages of drug development and marketing, and with a well-established trend in research policy that emphasises the role of public research as a stimulus and support for economic competitiveness and for the development of high-tech sectors considered both economically strategic and capable of creating highly qualified and well paid jobs.[14] Collaboration with the private sector has thus become a high priority of research policy and typically private companies take the lead in the last stages of converting research and knowledge into products and services. The biomedical sector is a very good example: after huge investment from public agencies and venture capital in the Human Genome Project, pharmaceutical industries have made conspicuous investments in pharmacogenomics, in part in response to a loss of productivity of their R&D activity (i.e. a lower ratio of new drugs reaching the market per money invested in R&D).[15]

Now that molecular stratification of diseases and disease causal pathways provide pharmaceutical industry with a range of potential targets for drug discovery, firms need to make choices about which research paths to pursue. Clearly from a business point of view there are three important criteria to consider: 1) the chances of success (i.e. how risky investing in this project is); 2) the magnitude of the reward in case of success (i.e. the magnitude and purchasing power of the target population and their insurers); 3) the likelihood of spillovers in terms of fur-

explanation of variations among groups; in practice, though, it has brought about "a pragmatic and value-laden acceptance of race as a proxy for individual genetic variation" (Jones [2011] p. 45, cf. Duster [2015]). This suggests that researchers may have a responsibility that goes beyond not deliberately pursuing racial medicine and requires that they actively take steps to avoid that, as an unintended consequence of their research, the concept of race becomes even more entrenched in medical practice.

[13] Ginsburg, Willard [2009]; Downing [2009]; Issa [2010]; Harvey et al. [2012]; Leyens [2014]. A useful analysis of the distributive justice implications of large research project led and substantially funded by public agencies can be found in Foster et al. [2006].

[14] The actual importance of pharmaceutical industry (as well as the actual extent of its investment) in drug development is probably overestimated and has been challenged by a number of studies. See for instance Goozner [2004] and Washington [2011] (chapter 2). On the expected economic role of the biomedical and biotech sector see for instance BIS [2010] and ESF-EMRC [2011]. For a critical appraisal of the impact of the biotech sector on health and the economy see Hopkins et al 2007.

[15] Langreth, Waldholz [1999]; Brody [2007]; Gassmann et al. [2008], Martin et al. [2013].

ther uses or developments of the drug (i.e. how likely it is that the drug may have other therapeutic uses or that this line of research may lead to further profitable discoveries). In short, what is the research direction that is likely to have the maximum payoff with the lowest risk? For private businesses aiming at furthering their interests and those of their shareholders, these principles are sound and are not unethical. It is also important to remember that large pharmaceutical industries will have a portfolio of research projects to diversify their offer and distribute their risk. Given these premises, it is very likely that diseases affecting small groups or mainly prevalent among poor or poorly insured populations will not be the preferred target for drug discovery and may remain orphan diseases, and yet it does not seem the pharmaceutical industry's responsibility to act for the benefit of the least profitable patients.

Rather than attributing to the pharmaceutical industries some sort of social responsibility that they do not seem well-suited to fulfil beyond some token gestures, it seems more promising to treat the undersupply of drugs for orphan populations as a market failure that we can try to correct through public policy creating the right incentives.[16] In fact, equity concerns about the unfortunate situation of patients suffering from rare diseases and neglected by pharmaceutical research have led to the development of special incentives for developing so called 'orphan drugs'.[17] The moral intuition at the basis of these policies seems to be that every individual is entitled to a chance to benefit from pharmaceutical research and advances. Since we cannot guarantee that any research effort will produce any effective result, the entitlement cannot extend to benefiting from results, but an ethical case could be made for creating the conditions under which no group of patients would be completely excluded from the research effort.[18] This equity concern can be ultimately grounded in more than one way. It can be derived from a basic right to equal consideration and non-discrimination, or from a basic right to health, or from a principle of social solidarity according to which no one should be left alone and neglected by the community: belonging to a moral community means belonging to a community of care and mutual support.

However, incentives for orphan drugs do not come without problems.

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[16] A reviewer observed that I gave short shrift to pharmaceutical industry corporate social responsibility. Perhaps it may achieve more than I have suggested, but the conclusions of Hunt, Khosla [2010] suggest that corporate responsibility alone is not sufficient and still needs to be supplemented through policy interventions.

[17] Goozner [2004] see in particular p. 46–47; Braun et al. [2010].

[18] As a reviewer noted, such an argument would be contested from some ethical perspectives. However, it is an attempt to articulate the ethical principles or intuitions underpinning the orphan drug legislation.

Simoens et al. [2012] have criticised both their ethical justifiability on the basis of people's preferences and their economic effectiveness, claiming that they themselves create new kinds of market failures. The economic criticism seems to be more effective, especially when we consider that the process of disease stratification and the creation of a new taxonomy of diseases may well multiply the number of rare diseases. So even if we believe that from the point of view of equity it is ethically appropriate to give special weight to the health needs of orphan populations that have been neglected, it is hard to understand how to effectively promote this goal. We should keep in mind that, as argued by Dudley and Luft, healthcare systems (and policies) have three fundamental goals:

> (1) to maximize the quality of healthcare available; (2) to minimize total national expenditure on healthcare; (3) to achieve equitable distribution of the benefits of quality healthcare and of the burdens of costs.[19]

So equity cannot be pursued at the risk of making the healthcare system unsustainable, which is what could happen if stratified molecular medicine were successful in fragmenting the taxonomy of disease and if pharmacogenomics were successful in delivering effective but expensive drugs for small groups.[20] Recent alarms on the economic impact of new treatments for hepatitis C, on the price of cancer drugs and on the price of a pharmacogenomic niche busters like Kalydeco, suggest that hyper-expensive drugs can have dangerous systemic consequences, and the prospect of their proliferation may be a curse (for healthcare systems sustainability) as well as a blessing (for patients benefited).[21] So incentives for orphan drugs need to be rethought in order to prevent abuses and make it financially sustainable.[22] This will require a difficult balancing of the claims of two classes of patients: those well served by the current medical technologies and treatments, and those who are not. The different interests of these groups can be effectively illustrated by how they would prioritise between investment in healthcare and investment in biomedical innovation. Orphan patients clearly would prioritise innovation, while patients who benefit from existing treatments would prioritise expenditure in healthcare. Solving this conflict of priorities takes

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[19] Dudley, Luft [1999] p. 706.

[20] Rai [2002] has foreseen this risk and observed that the likely emergence of new genomic orphan groups will force to reconsider orphan drug legislation and to introduce priority setting procedures (like cost-benefit analysis) to allocate scarce resources for orphan populations.

[21] On Kalydeco see O'Sullivan et al. [2013]; on the price of cancer drugs see CML [2013]; on the price of the treatment (Sovaldi) for hepatitis C see Sachs [2015].

[22] Wellman-Labadie, Zhou [2010]; Gibson, Tigerstrom von [2015]; and Herder [2017].

us outside the well-researched field of allocation of scarce medical resources and opens a new domain for bioethical enquiry in which choices involve trade-offs between predictable and hypothetical benefits. It also forces us to decide whether the current healthcare to research investment ratio needs to be corrected in order to achieve a fair balance between different demands.

An end-state analysis of the distributive effects of pharmacogenomics stratification

In the previous section we have followed some of the key steps and decisions that may lead to a development of pharmacogenomics that fails to produce a fair distribution of its benefits.[23] Although necessarily simplified, the reconstruction suggests that the uneven distribution may result from choices that are legitimate and reasonable from the point of view of researchers, firms and policy makers and that they do not imply any intention to discriminate against any group.

There are a few other arguments for not considering these inequalities of real moral relevance. The first argument is that drugs have always brought unequal benefits to different patients: the fact that some people benefit and other do not, that some people have serious side effects and other do not, has always been there and is not peculiar to pharmacogenomics. If this difference in bringing benefits and harms has not been considered morally problematic before, what makes it more salient now? It is not easy to address this objection. The most obvious difference is that the reactions of different patients were hardly predictable, while now genomic and other molecular analyses provide much more accurate ways of predicting outcomes. Still, at the level of drug prescriptions this does not seem to entail any moral wrong: now it is possible to provide drugs to those who can benefit and to save from severe side effects those who are predisposed to suffer from them; these are therapeutic choices dictated by beneficence and nonmaleficence, so there are no moral problems. Alternatively, if one adopts a view of medical need as a capacity to benefit, these distributions seem perfectly sound: we give to those who can take advantage of a treatment and not to those who cannot.[24] But from

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[23] A discussion of the distribution of the burdens would need to be broader and would have to carefully consider questions about the distribution of resources between different programmes of research and healthcare. In other words, it would have to consider whether an expensive programme, like that of human genetics and genomics, and their medical applications, like pharmacogenomics, are justified in terms of opportunity costs, i.e. in terms of resources that they take away from alternative research and healthcare or public health programmes. These are very important questions, but cannot be broached here; a very good starting point on this issue is Fleck [2014]; see also Martin et al. [2006] section 5.3; James [2014]; Bayer, Galea [2015]; Khoury, Galea [2016].

[24] For a good discussion of the possible interpretations of "need" in healthcare see Culyer, Wagstaff [1993].

our previous discussion we know that the problem is upstream, with the research and development of pharmacogenomic tests and drugs. Here the problem seems to be that in front of comparable claims of need—and in this case need has to be understood as ill health, for in terms of the capacity to benefit orphan patients have no need!—coming from different groups of patients, not only we do not have enough resources for doing all that we are capable of doing, but we are also faced with requests to broaden the spectrum of what we can do. We are capable of doing more than we can financially afford to do, and yet this does not sound like a good reason to dismiss the call for help of those who can only hope in new discoveries. Once biomedical innovation is brought into the picture, denying that medical conditions non treatable generate some claims that need to be heeded seems to be a hardly defensible position. In an age of growing biological and biotech knowledge and powers, the domain of resource allocation expands to include future (speculative) possibilities. We have more than we can afford but not yet all that we need: choices and their justification are even more difficult.[25]

At the level of publicly funded research programmes we can follow Foster et al. [2006] and agree that in making research choices and design there are different values to be balanced, for we can either try to address those needs that cause the greatest burden of disease (whether at a national or international level is another important question that cannot be addressed here), or we can give priority to the needs of those that are more disadvantaged (and here too there is a complicated choice to be made between socio-economic disadvantage or biomedical disadvantage). This choice reflects the familiar alternative between the utilitarian choice of pursuing maximum aggregate utility and the Rawlsian choice of giving priority to the worse off. Furthermore, Foster and colleagues point out another value, namely the greatest scientific significance and the possible greater benefits coming from aiming at breakthroughs that seem to be within reach; to me this goal seems to align quite well with the goal of minimising the burden of disease. While the maximisation of health benefit and prioritisation of the worse off point to different research agendas, it is possible to elaborate mixed strategies that impose some equity constraints to the goal of maximisation, thus balancing the two.

At the level of pharmaceutical industry, choices look more disturbing because inequalities stem from attempts to maximise profit.[26] But here it could

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[25] As a result, careful assessment of alternatives is paramount and it should be noted that the actual clinical effectiveness and cost-effectiveness of pharmacogenomic products that have reached the market and the clinic is currently an issue at the centre of controversies. See for instance Evans, Khoury [2013]; Janssens, Deverka [2014]; Drew [2016]; Prasad [2016].

[26] Cf. Smart et al. [2004] p. 327–328.

be pointed out that the same unequal outcomes could be produced if at the trial level a drug developed for the general population proves effective only for a genomically specified subpopulation. Here of course the profit motive is not involved since it would actually be more profitable to keep the general population as a target for the drug. But the profit motive is not *per se* immoral, and if it is used to determine which genomic group to benefit when not all can be benefited, it does not seem to me particularly objectionable—if I can help either A or B but not both, other things being equal, choosing on the basis of my own payoff is not wrong. Nevertheless, we can still have a feeling that choices that can be as important as to determine who will be cured and perhaps even saved from death (well, momentarily), i.e. choices that decide our fate, should not be left to the logic of the market. However, all in all, it seems that the fact that now who will benefit from a drug and who will not can be predicted in genomic terms does not make a real moral difference, unless it is accompanied by the explicit intention to discriminate or exclude some groups.

Another argument in defence of the unequal distribution of pharmacogenomic benefits comes from considering the interests of future generations. It may be argued that future generations have an interest in our promoting a sustained level of biomedical innovation, so that they will benefit from our discoveries. Furthermore, it can be argued that there is a sort of symmetrical but not reciprocal obligation between generations: each benefits from the scientific advances of previous generations and ought to contribute to increasing the stock for future generations. Now, it is not implausible to argue that the rate of innovation will benefit from a high level of private investment in R&D and that these will only be forthcoming if they are attracted by the prospect of good profits. In the future, when patents expire, benefits will be distributed more equally. Of course, this more equitable distribution does not affect those for whom drugs are not developed, but nonetheless it can be argued that objecting to the interference of the profit motive now may have the effect of considerably reducing the amount of useful innovations available to future generations. In other words, it is not denied that there is and will be unequal distribution of benefits, but that this is the result of the combined effect of our limited resources and of biological hurdles, not of the profit motive, and that this latter actually maximises benefits (although not equity in distribution) for future generations.

Are these arguments enough to put to rest our worries about the distribution of the benefits of pharmacogenomics? It seems that the moral intuition that there is something wrong with such an outcome cannot be so easily dispelled. This moral uneasiness has been voiced by many authors, consider for instance the

words of Karen Peterson-Iyer:

> The idea that someone or some group would enjoy significantly less access to medical treatment simply by virtue of race or economic status, or even by their "draw" in the genetic lottery, violates a deep seated sense of fairness.[27]

There is little doubt that the possibility that genetic differences substantially overlap with racial distinction and may therefore be used to further discriminate groups that already have suffered a history of injustices is a serious worry that needs to be addressed. Avoiding any unequal distribution of benefits that exacerbates existing injustices seems to be a strong moral requirement that would demand very compelling justifications to be overridden.[28] So we have established a first ethical limit to the acceptability of pharmacogenomics-generated inequalities: they are unacceptable if they reinforce previous discriminations and social exclusion for disadvantaged groups.

Is there anything more to be done to moderate the arbitrariness of the "genetic lottery"? Perhaps something can be done. I assume that the moral iniquity of the uneven distribution of benefits is not so great and offensive as to justify a radical solution that would take drug R&D away from private firms and under a regime heavily controlled so as to produce fair results. Such a solution would be actually impracticable, and disproportionate, for a) it will not solve completely the problem, given that some of the arbitrariness of the benefit production depends on biological factors beyond our control, b) it would lose private investment and thus either impose a much higher burden on the public purse or cause a considerable downsizing of drug R&D activity and benefit production, c) it would curtail some important economic freedoms. A more modest approach to the mitigation of iniquity is nevertheless available. Before sketching it, let me restate the moral issue in a different framing.

Distributive equity in time and solidarity

Biomedical research is meant to push forward the limits of what is possible to do in order to help the sick. Biomedical advances are in part the result of luck and serendipity and in part the result of human choices and concerted invest-

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[27] Peterson-Iyer [2008] p. 38.

[28] See Braveman [2006] for a philosophical defence of this position. See Cohn, Henderson, Appelbaum [2017] for a discussion of the practical challenges, for instance of including all groups in trials, and for a list of distributive justice questions raised by Precision Medicine still waiting for satisfactory answers.

ments and efforts. Let us assume that luck and serendipity fall outside the domain of ethical and political assessment, while human decisions and research strategies, objectives and priorities do not. When societal resources are deployed to change what is possible to do in order to help the sick, decisions about their allocation and the strategic goals pursued need to be justifiable to the public. One key reason why such a justification is needed is that those decisions will affect whose misfortune will be alleviated and whose will be left unchanged. In other words, societal action will improve the lot of some citizens while it will leave unchanged the lot of others: it creates differences that are far from inconsequential. Now consider the following analogy. Suppose that a country, because of climate change, is experiencing a much higher risk of flooding. It is therefore decided to start a plan for embanking rivers in the attempt to secure the safety of citizens. Resources being limited, it is decided that the programme will start by embanking rivers around large cities, and then in other densely populated areas, while in some other areas no work will be done either to leave some wilderness areas untouched, or because in some areas the work would not be cost-effective and having evacuation and compensation plans will be a more effective choice for protecting local citizens.

The analogy with protecting citizens from flooding directs our attention to some important points. The first is that difficult issues of distributive justice in society need to be considered and tackled as spanning over time, i.e. from a diachronic perspective. The goal is to benefit all equally, but in practice this is seldom possible and some people will get benefits before others. This is acceptable in the context of a strategy that in time aims at protecting all, and that gives compensations to those who are excluded from the benefits. So, coming back to our pharmacogenomics case, the analogy suggests that we can accept an uneven distribution of benefits in the initial stage of development of this scientific programme and of its clinical translation, but on condition that there is a plan for proactively pursuing a more egalitarian and widespread distribution of the benefits as the technoscience behind pharmacogenomics develops and becomes mature. This could be achieved by concentrating on the low-hanging fruits in an initial phase, so as to allow knowledge to grow, technologies to mature and private capital to be attracted by the prospect of possible profits. But there should be a commitment that in a following phase investment should be directed to even out the distribution of benefit. This could be done both by working on the supply side—investing in research on neglected diseases and populations—and on the demand side—for instance through drug coverage policies that give a premium value to drugs effective for neglected diseases or populations. Furthermore, it should not be forgotten that it is unlikely that all will benefit even at a later stage. Therefore, while money

is invested in developing pharmacogenomics and in covering the successful (i.e. clinically effective and cost-effective) discoveries that come into the market, a suitably commensurate investment should be made to take better care of those who cannot be cured, for instance by providing them with better palliative care, and support services. In order for the investment to count as commensurate, it should produce benefits that are noticeable and valued by patients, so as to give them the sense that their needs are not ignored and completely sacrificed for the benefit of other groups of patients.

The proposed approach combines elements of welfare maximisation, efficiency and commitment to promoting innovation for the sake of future generations, with concerns for equity and social solidarity. A tactical sacrifice of equity is allowed in the context of a long term strategy that will later focus on equity, and in combination with the provision of valuable compensations. In the absence of the proposed compensations, it would be hard for people neglected by pharmaceutical R&D not to feel short-changed and let down. But if some other form of support and alleviation of their condition is offered to them, together with the commitment that in future the good of those suffering from their disease or having their genomic profile (e.g. a group that is a poor respondent to existing drugs) will receive special attention, they can come to see that it is because of a necessity to make tough choices and optimise the use of limited resources that their needs are currently put in the back burner, not because they are considered less important. Once this is appreciated, solidarity can plausibly be understood as demanding that they acknowledge that the strategy is a reasonable compromise to promote the long-term interest and wellbeing of society and that they should thus accept it.[29]

Conclusions

Let me now summarise the main conclusions that I have tried to argue. First of all, it is important to remind the reader that this paper is *not* meant to offer a comprehensive overview and appraisal of the ethical issues raised by pharmacogenomics. On the contrary, it has isolated only one ethical problem, namely the fact that the benefits of pharmacogenomics will not be distributed equally and evenly among the population and genomically defined orphan populations will be created. The fact that I have focused on this particular issue does not mean that

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[29] I believe this is compatible with the definition of solidarity proposed by Buyx, Prainsack [2017] p. 52, as "an enacted commitment to carry 'costs' (financial, social, emotional, or otherwise) to assist others with whom a person or persons recognise similarity in a relevant respect."

I consider other ethically problematic aspects less important: they are not less important. To stress this fact, I will shortly mention two of them and how their consideration could be added to the strategy to tackle the problem that I have considered.

I have addressed the question whether the unequal distribution of the benefits of pharmacogenomics makes the development of this medical technology ethically unacceptable. I have shown that under existing biological diversity and limits of knowledge and resources, uneven generation of pharmacogenomic benefits does not need to be the result of any discriminatory intention, but is the product of the pursuit of promising scientific advances in the context of public-private collaboration and division of labour that need to make room for the profit motive. However, this does not mean that the current distribution of burden and benefits between public and private partners and the population is working as well as it should, but this is the topic for another paper. This system of doing biomedical R&D is not perfect, but the kind of inequalities generated by pharmacogenomics do not seem to be so offensive as to demand the demise of the system. Nevertheless, there are some genuine equity issues that cannot simply be accepted as a lesser and necessary evil. I have thus argued that any production of pharmacogenomic benefits that exacerbates inequalities associated with past unethical discriminations and marginalisation are not admissible, for they create more harm in terms of social injustice, division and hostility between groups than medical benefits. I have further argued that while uneven distribution of benefits can be temporarily accepted, this acceptance is only justified on condition that a) there is a long-term commitment to attempting to even out these inequalities and b) meaningful alternative benefits in term of support and palliation need to be set up for those who are temporarily or forever excluded from benefiting from pharmacogenomic innovations.

My argument has thus produced an acceptance of the inequalities produced by pharmacogenomics, qualified by two important provisos. Now I want to briefly suggest that more provisos or conditions of acceptability for pharmacogenomics may be added when other issues pointed out in the literature are considered. In footnote 23 I have hinted at the important issue of the burden of pharmacogenomics in terms of opportunity costs: are we sure that public money spent on financing genomic research and on facilitating the development and translation into clinical use of pharmacogenomic products would not be better spent in other healthcare and public health activities?[30] If this question has some strength, as it

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[30] Joyner, Paneth [2015]; Bayer, Galea [2015]; Khoury, Galea [2016].

seems to be quite plausible, it would be possible to add another proviso to the acceptance of pharmacogenomic inequalities, for instance that it should not generate what we could call inverse care law effects, i.e. to shift healthcare availability further away from those more in need for the benefit of those social groups that already have more access to it.[31] Similarly, it has been noted that by aiming at performing more targeted trials (i.e. trials performed on smaller and more genomically homogeneous cohorts) pharmacogenomics will affect the distribution of risk among patients, for in the real world the use of drugs is not always in conformity with therapeutic indications. So, smaller and targeted trials may exacerbate the already existing problem of the limited representativity of many trials because of recruitment and selection criteria.[32] This problem of the exclusion of many groups of people from trials might become even worse and increase the number of populations unrepresented in trials and hence exposed to higher risks. If these worries are well grounded, another proviso aimed at preventing such outcomes may be added. And this process can go on to consider all other ethical concerns raised by pharmacogenomics. My point is that, while very limited in scope, my analysis can be taken as a skeleton to which much flesh can be added.

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[31] On the application of the idea of the inverse care law to genomic medicine see James [2014].

[32] Rothstein, Epps [2001]; Issa [2002]; Smart et al. [2004]; Cohn, Henderson, Appelbaum [2017].

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