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Global Implications of Personalised Medicine

Global health challenges and personalised medicine*

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Resum. El 2001, el Banc Mundial va assenyalar que el problema més gran que la humanitat afrontaria en el segle XXI seria la pobresa. Avui dia sabem que 1.200 milions de persones, aproximadament una cinquena part de la població mundial, viuen amb menys d'un dòlar al dia i que les malalties transmissibles continuen representant la meitat de les morts i gairebé dos terços dels anys de vida ajustats per discapacitat (AVADs) entre el 20 % més pobre de la població mundial. Des d'una perspectiva de salut global, es tracta d'una bretxa d'equitat en salut inacceptable. Si els medicaments i les mesures preventives existents fossin més accessibles, ara mateix podrien salvar milions de vides. Alhora, la investigació de nous medicaments i vacunes, i llur desenvolupament clínic posterior, són essencials per a obtenir munició eficaç contra les malalties que mantenen les persones en situació de pobresa. A la vista d'aquests reptes per la salut global, cal que els potencials beneficis de la medicina personalitzada compleixin avaluacions basades en la investigació, incloent la utilitat clínica, el baix cost i la factibilitat tècnica, en el marc de sistemes de salut prou sòlids, i amb personal degudament capacitat. Cal potenciar els partenariats amb països de baixos i mitjans ingressos, amb el suport del Programa Marc Horitzó 2020 de Recerca de la UE.

Paraules clau: medicina personalitzada · salut global· malalties relacionades amb la pobresa · equitat en salut

Summary. In 2001, the World Bank stated that the biggest problem facing humanity in the 21st century would be poverty. Today, we know that 1200 million people, about a fifth of the world's population, lives on less than a dollar a day and that communicable diseases continue to account for half of the deaths and almost two thirds of the disability-adjusted life years (DALYs) among the poorest 20 % of the world's population. From a global health perspective, this is an unacceptable health equity gap. If the existing medicines and preventative measures were made more widely available, they could already save millions of lives. At the same time, research into new drugs, vaccines, etc., and their subsequent clinical development are crucial to obtaining effective ammunition against diseases that keep people in poverty. In the view of such global health challenges, the potential benefits of personalised medicine need to meet research-based evaluations, including clinical utility, low-cost and technical feasibility, within responsive healthcare systems with adequately trained personnel. Partnerships with low and middle-income countries, with the support of the incoming EU Horizon 2020 Research Framework Programme, need to be promoted.

Keywords: personalised medicine · global health · poverty-related diseases · health equity

First, I would like to briefly describe the Barcelona Centre for International Health Research (CRESIB). CRESIB's mission is to find solutions to current and future global health challenges. It was established in 2006 by a group of first-rate academic and biomedical research institutions (the Hospital Clínic de Barcelona, the University of Barcelona, and the August Pi i Sunyer Biomedical Research Institute) and by the Government of Catalonia. More recently, in 2009, with the support of the "La Caixa" Foundation, CRESIB became the research arm of the Barcelona Institute for Global Health (ISGlobal). This institution is the fruit of an innovative alliance between academic, government, and philanthropic organizations. It seeks to provide a hub of excellence in research and healthcare that will help close the gaps in health disparities between and within different regions of the world. It includes a think tank, aimed at the management of knowledge and designed to influence policy; a training centre, aimed at the transmission of knowledge, and a technical assistance centre, aimed at the application of knowledge. In 2013, ISGlobal and CRESIB signed an agreement with the Centre for Research in Environmental Epidemiology (CREAL) to become a world-leading alliance in the field of global health.

CRESIB carries out multidisciplinary and translational research in molecular biology, physiopathology, immunology,

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clinical characterization, and epidemiology, as well as in the clinical development of treatment and prevention tools, such as vaccines. Gradually, we have pursued downstream approaches with the monitoring and evaluation of public health. Broadly stated, our goal is to improve global health through research and training, with our main areas of work focused on malaria, imported diseases, HIV/AIDS and STDs, viral and bacterial infections, and other emerging disease-related activities. We use a cross-sectional approach, including public health, social sciences and medical anthropology, maternal, child and reproductive health, and host-pathogen interactions.

Finally, one of the main features of our efforts is that we collaborate with more than 100 institutions from 40 countries across the five continents, including stable partnerships with high quality research capacities in low-income countries such as Mozambique, Morocco, and Bolivia. As such, ISGlobal is a centre committed to translating research into action.

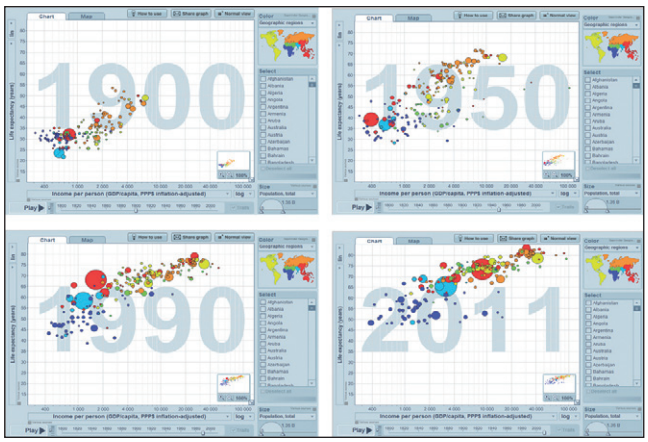

Fig. 1. Correlation between life expectancy (years) and income per person (GDP per capita, PPPs inflation-adjusted) in 1900, 1950, 1990 and 2011. Source: Gapminder [www.gapminder.org]

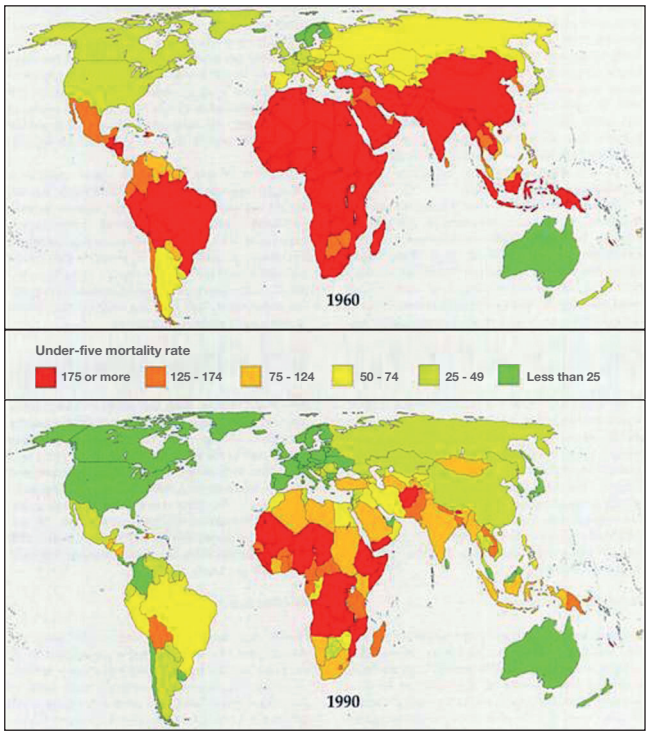

Fig. 2. Child mortality by country, 1960 and 1990. Child mortality has fallen sharply in the past 30 years, with particularly rapid declines in parts of Asia and Latin America. Source: World Bank [5].

The global health vision

One way to define Global health is 'public health without borders.' More specifically, this means:

- Better health for all, taking into account current disparities and inequalities, with particular attention to the needs of the most vulnerable; in other words, health as a human right.
- A global perspective on both scientific inquiry and the translation of knowledge into practice.
- A scientific approach to health promotion and disease prevention, examining broad determinants of health, including but not limited to, medical care.
- An interdisciplinary approach and collaborative team work that includes population problems analysis.
- Multilevel systems-based interventions: society, governance, corporate responsibility, environmental, behavioural, and biological risk factors.
- Comprehensive frameworks for financing and structuring health policies and services that support community-based and clinical prevention integrated with healthcare delivery. [2]

Within this approach, I would like to emphasise the issue of equity, because if we talk about a global health point of view, the major challenge facing humanity is the unacceptable health equity gap. Indeed, today, in the 21st century, our life expectancy is still largely determined by where we are born.

Figure 1 shows the distribution of income as well as life expectancy in different countries over time. At the beginning of the last century, in the 1900s, life expectancy varied worldwide, from about 25 to approximately 50 years, but with relatively little difference either in life expectancy among countries or in terms of per capita income. In the 1950s, the spread became quite substantial. For some countries, those shown in blue, and specifically many African countries but also some East Asian countries, there was very little change during those 50 years. In the 1990s, the spread continued to increase, with some of these countries starting to move up, not so much in terms of income but rather in life expectancy. Finally, there is currently good and bad news. The good news is that in African and East Asian countries, as in most countries, life expectancy has steadily improved; but the bad news is that, overall, discrepancies among countries have increased, ranging from less than 50 years for in some low-income countries to more than 80 years in high-income countries.

For example, in the mid-20th century, a very large part of the world had infant mortality rates that were quite high, between 15 and 20 ‰ (per thousand). Fifty years later, at century's end, the picture had for the most part changed completely, with a reduction of more than 100 % (Fig. 2). So this is the good news.

Table 1. Distribution of child deaths for selected causes by selected WHO region, 2004*

	Africa	South-East Asia	Rest of the World
All causes	45 %	30 %	25 %
Diarrhoeal diseases	45 %	35 %	20 %
Pneumonia	50 %	25 %	25 %
Malaria	90 %	5 %	5 %
HIV/AIDS	90 %	5 %	5 %
Measles	45 %	45 %	10 %

*Percentages rounded to the nearest 5 %. Source: World Health Organisation [7].

But if we look at the data on a regional basis, we see that although infant mortality has improved in all regions, there are large differences among them. For children under the age of five years, mortality has decreased overall, but the worst rates are still those of the African continent.

The 20th century Smallpox was eradicated, while we are not far from the eradication of polio and measles. There has been a decrease in overall mortality and life expectancy at birth has increased substantially, by 25 years on average. Mean individual wealth has also increased at an unprecedented rate, accompanied by a very strong technological revolution. These achievements are proof that with effective strategies and the proper involvement of governments, industries, scientists, etc., we can achieve success on a scale never seen before in the history of humankind.

But, is all the news genuinely good? Not really. Today, we know that 1200 million people, about a fifth of the world's population, lives on less than a dollar a day and that communicable diseases continue to account for half of the deaths and almost two thirds of the disability-adjusted life years (DALYs) among the poorest 20 % of the world's population. And for children around the globe, infectious diseases, such as diarrhoea, pneumonia, malaria, HIV/AIDS and measles, account for a substantial share of these figures (Table 1). Again, Africa and Southeast Asia suffer the highest share of this burden, largely because of the impact of infectious diseases.

In 2001, the World Bank stated that the biggest problem facing humanity in the 21st century would be poverty. Disease generates poverty, and poverty generates disease. Nonetheless, the positive view of the situation, is that the percentage of people living on less than 1.25 US$ a day—that is, in extreme poverty—has decreased by half (from 43 % to 22.4 %). In fact, while in 1990, 1.9 billion people lived in extreme poverty, by 2008 the number had decreased to 1.29 billion. But it is important to remember that this improvement has been very unequally distributed throughout large parts of the world. Both in Africa and in some Asian countries, a majority of the population still lives in extreme poverty, which means an especially high risk of many diseases, and not just infectious diseases (Fig. 3).

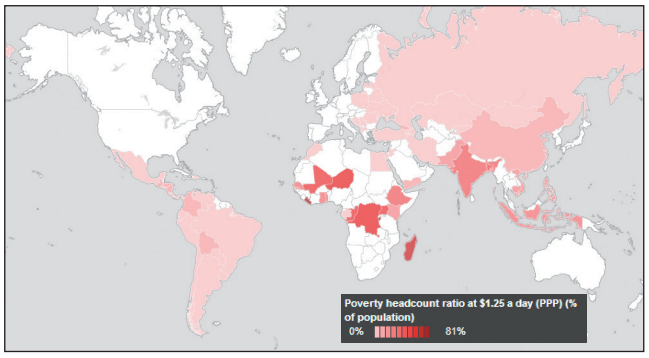

Fig. 3. Percentage of the population living on less than 1.25 US$ a day at 2005 international prices. Source: World Bank [6].

Former US Secretary of State General George C. Marshall, responsible for the Marshall Plan, the American program of aid to Europe after WWII, said over half a century ago, in 1948, that,

> "Little imagination is required to visualise the great increase in the production of foods and raw materials, the stimulus to world trade and above all the improvement in living conditions, with consequent social and cultural advances that would result from the conquest of tropical diseases." [4]

As shown in Fig. 4, which lists the leading causes of death by income group, in low income countries, infections of the lower respiratory tract are the first cause of death, whereas ischemic heart disease is the most frequent cause worldwide and in high income countries. Nonetheless, cerebrovascular diseases (stroke ischemic heart disease) already rank among the ten major causes of death at all ages in low income countries, curiously mimicking the situation in the world as a whole and in some high-income countries. The same is true for some infectious diseases. But, in general, diseases of poverty continue to account for a large share of deaths. Furthermore, most countries are experiencing an epidemiological and behavioural transition, i.e., in addition to the burden already posed by malnutrition and communicative diseases, there is the growing burden of non-communicable, so-called chronic diseases.

At the same time, the major disease determinants or risk factors are increasingly similar in low income as in high income countries. Many of these risk factors are largely amenable to environmental interventions. Thus, we already have the knowledge that can help us to confront globally many of these risks. It is also important to keep in mind, from this global perspec-

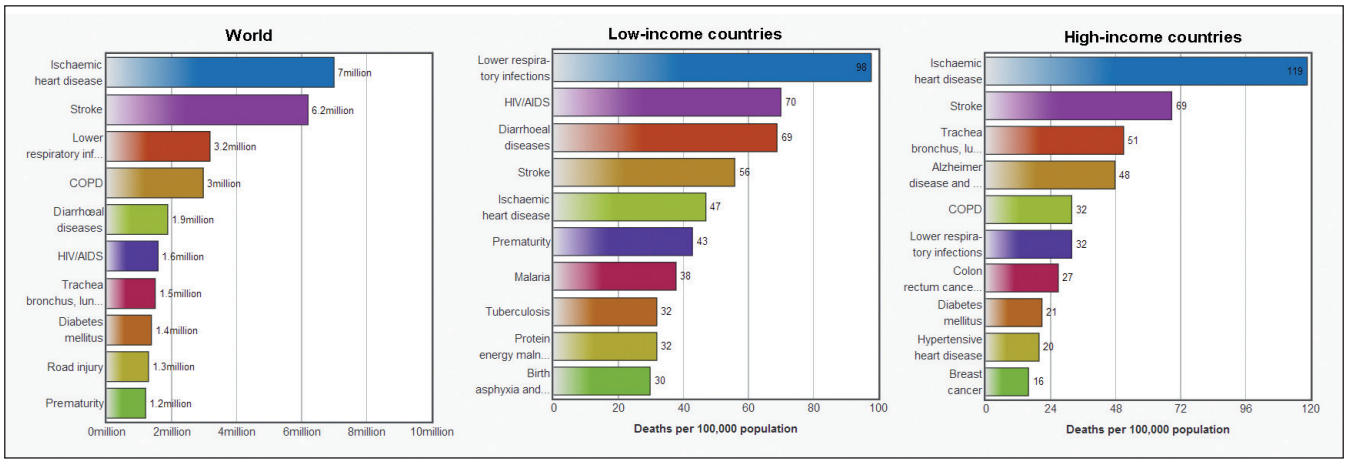

Fig. 4. Top ten causes of death in (A) low income countries vs. (B) high income countries, 2011. Source: World Health Organisation.

tive, that there is a lack of equity in the provision of health care services. One of the classical examples is maternal mortality, a good indicator of the access to primary or obstetrical care or the lack thereof with more than ten-fold differences among countries. Again, the issues of poverty and the inequitable distribution of different diseases are highly relevant.

The role of research in global health

The role of research in global health is a longstanding one. Figure 5 is a very interesting British cartoon from the 1920s that depicts malaria draining the life out of tropically based industries, including tea, coffee, vegetable oil, and copper; that is, several of the main sources of revenue for the British Empire. The work of Sir Ronald Ross, who received the 1902 Nobel Prize for his work on malaria, and the Ross Institute and Hospital for Tropical diseases were already seen as means to avoid or at least to minimise the devastating impact of malaria—and by extension of other infectious diseases—on business and the economy. The concerns depicted in the cartoon are still very familiar ones today, i.e., high costs and low efficiency, and implicitly emphasise the important role of research in global health to contribute to a productive economy.

If they were made more widely available, the existing medicines and preventative measures for the above-mentioned diseases could already save millions of lives, although none of them can completely eliminate HIV/AIDS, TB, or malaria. At the same time, research into new drugs, vaccines, etc., and their subsequent clinical development are crucial to obtaining effective ammunition against diseases that keep people in poverty. Yet, of the 1233 new drugs that reached the market between 1975 and 1997, only 13 were for tropical diseases primarily affecting the poorest populations. This is known as the "10/90 gap" and, while not a real quantitative measure, it has become a symbol of the continuing mismatch between global health needs and the investments to meet them. Indeed, investment studies by the Global Forum for Health Research (www.globalforumhealth.org) continue to demonstrate that "health research applied to the needs of low- and middle-income countries (LMICs) remains grossly under-resourced in many areas".

Potential for personalised medicine in global health

So how can personalised medicine contribute to global health? On the one hand, overall, we humans throughout the world are probably much more genetically similar than different. While this is a very broad statement, it is meant to point out that many of the findings obtained by research in wealthy countries can be generalised to the whole world. But to what extent do these one-size-fits-all strategies meet our needs? We are at the early development stages of both personalised medicine and the different '-omics.' Thus, we need evidence-based medicine and research into the comparative effectiveness of newly developed therapies if we are to make informed decisions in this area.
So what are the real benefits of personalised medicine and what are the prospects for LMICs? The answers to these questions are closely linked to the need for research aimed at meeting those challenges through, for example:

- Better or targeted interventions, vaccines, or drugs; here, *vaccinomics* is an area of potential interest.
- Diagnostic, screening, or predictive tests.
- The need for firmly established research and care capacities (laboratory genomics, biobanks, epidemiologic cohort studies, clinical studies, randomised control trials, gene-based technologies, etc.)
- Collaborative research involving investigators from low and middle income countries and high income countries, including multidisciplinary and public-private partnerships.
- Need for training and education of the workforce.
- Ethical and legal frameworks.
- Equity of access. [3]

Accordingly, is personalised medicine, from a global health standpoint, a priority? Most of the targets for public health in-

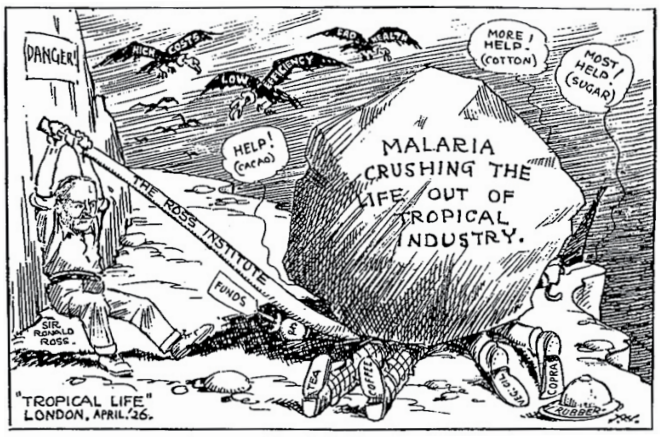

Fig. 5. Appeal in 1926 for subscriptions to funds for research on tropical diseases (From 'Tropical Life', London).

terventions, as described, are on the environmental side, with different strategies and stakeholders, including economic, social, and political ones. There is also a predominance of risk factors that are amenable to environmental modification. At the same time, we cannot forget that these strategies are likely to be effective for most of the previously discussed risk factors, such that the aim is to promote a more equitable provision of health services. Many of LMICs have very limited resources for health services and their distribution tends to be inequitable, which raises issues of global justice and human rights. It has been pointed out that:

> "A major challenge is to generate an evidence base that can demonstrate that a genomics approach is at least as safe, effective and cost effective in these settings as other, more traditional approaches, such as modifying environmental or social determinants." [1]

In this context, are there precedents of potential interest? Here we need to consider:

1. Areas with clearly established evidence of clinical utility, for example, the prenatal or neonatal detection of certain inherited diseases.
2. Areas with currently available low-cost solutions, for example, the more systematic use of family history information.
3. Areas with the scope for targeted innovative technical solutions, especially regarding prevalent infectious diseases.

In general, there is a need for a public health genomics approach that is applicable to all countries but at the same time relevant on a smaller scale. Here, efforts should include selecting evidence-based applications, maximizing heath benefits and reducing inequities, reducing harm and unnecessary healthcare expenditures (premature or inappropriate use), evaluating public health interventions, and fostering capacity building in research and clinical care.

When we talk about personalised medicine and global health challenges we are also talking about the ability to enlarge the scope of research to include partnerships among low, middle-, and high-income countries. Only through such partnerships will we succeed in introducing whatever benefits or effective innovations come of them in order to improve global health. As an example, for over twenty years, the Clínic Foundation, Barcelona, and the Spanish Agency of International Cooperation have partnered with the Health Research Center in Manhiça, Mozambique. The initial focus was malaria, but the partnership has expanded to other areas and is now part of a research network of African centres.

Global health R&D on the near horizon?

As a final point, let me underline that efforts have been made to include the topics of global-poverty-related and neglected diseases in the next EU Research Framework Programme, Horizon 2020, and in the relevant discussions of the European Parliament and the European Commission. Market forces alone will not lead to the development of sufficient, affordable, and appropriate new technologies and goods for these diseases. Public support and public financing are required when public goods are under-supplied by the market, as is the case for drugs used in the treatment of malaria, TB, and HIV/AIDS, several of which were effectively introduced over the last decade in many developing countries. Horizon 2020 presents an opportunity for the European Union to step in as a leader in addressing market failure and in stimulating innovation.

It is crucial to raise awareness and to mobilise members of the European Parliament and EU policy-makers in supporting stronger EU investment and commitment—both political and financial—in the fight against poverty-related and neglected diseases. This also means raising the issue of the cost-effectiveness of investing in R&D for global health and the potential of innovations in this field to for strengthen Europe's research leadership.

Why? Basically because we can also strengthen the EU economy through support for an essential but challenged area of European innovation, by providing a competitive advantage for European industry and research. Improving the health not just of Europeans but globally will have positive effects on health systems, employment, and global health security. It can also contribute to sustaining the credibility of the EU in its commitments, made through a wide range of EU policies including those on health, economic growth, social inclusion, and development. Global health efforts can facilitate progress in other areas, such as science diplomacy, knowledge sharing, and common solutions to problems.

I end this contribution with a quote appropriate to this global approach to science, from India's first Prime Minister, Jawaharlal Nehru (1889–1964), considered the architect of this developing country's modern nation-state,

> "Who indeed could afford to ignore science today? At every turn we have to seek its aid... The future belongs to science and to those who make friends with science."

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