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Precision medicine: Beyond AI

Marco Filetti [a,b], Manuela Petti [c,*], Lorenzo Farina [c,d]

[a] Phase 1 Unit, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy
[b] Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy
[c] Department of Computer, Control, and Management Engineering, Sapienza University of Rome, Via Ariosto 25, Rome 00185, Italy
[d] PhD. Program in "network oncology and precision medicine", Sapienza, University of Rome, Italy

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Twenty years have passed since the completion of the genome project, the sequencing of the coding part of human DNA. The clinical impact of this remarkable collective endeavor is now evident, for example, by a series of new therapies that target misfolded proteins due to mutations in the corresponding gene. Paradoxically, the great merit of the genome project lies in its revelation of our profound ignorance concerning the mechanisms that govern life and disease.

The path from genotype to phenotype remains largely unexplored, because we may only know a few tiny, sporadic features here and there. Understanding the DNA sequence and its mutations is a very small part of the story. In fact, while targeting mutated proteins can lead to tumor elimination in certain cases, personalized treatments may provoke resistance in rapidly mutating cancer clones that evade the initially "targeted" attack and give rise to more aggressive variants.

The message is therefore loud and clear: every complex disease, such as tumors, has a long history and a tortuous path of causes and effects that interfere with each other in the most intricate ways, but ultimately it presents itself with the typical characteristic of a living organism: its absolute and disarming uniqueness.

The molecular, pathological and clinical characterization of this complex uniqueness is precisely the original dream of "precision medicine", an innovative approach that aims to "deliver the right treatment, at the right time, to the right person, every time" [1]. Despite the challenges and setbacks, the dream persists. The reason is that we now have much more data than in the past: a whole range of health-related measurements that allow us to study and describe diseases using different level of investigation such us DNA, RNA, proteins, metabolites and medical imaging. Consequently, therapy could be tailored with utmost precision. Proof of this is the fact that in oncology in recent decades we have learned that each cancer is defined not only by location and histological type, but also by genomics [2].

The turning point

The healthcare industry has not been immune to this wave of advancement. Artificial intelligence (AI) seems to have won over physicians and investors worldwide because of its usefulness for applications such as virtual telemedicine support, diagnostic imaging, automatic generation of medical history summaries, and many others [3-5]. However, there are some concerns regarding the adoption of AI and machine learning into clinical practice due to the limitation in the generalizability of findings across clinical trials [6]. But is it merely a matter of data size, diversity, sophisticated algorithms, and powerful computing tools? Can we really rely solely on AI to diagnose and treat complex diseases? Or is there more to it?

This is the crucial point: if we view a disease like a puzzle or a Rubik's cube, with our data representing its pieces, then finding a cure becomes a matter of "calculation" or following a "protocol." However, if we are dealing with a disease that is unique in some essential way, can we use data and calculations to imagine the unknown that lies ahead? There is a widespread belief that "the truly new" does not exist, and that the supposed novelty is only the result of our ignorance, and that therefore with more data and more computing resources we would still be able to solve the puzzle, no matter how big. Of course, this is possible, but unfortunately it is an unfalsifiable statement, an act of faith, because we will never know if we have "enough" data and "enough" computing

* Corresponding author.
E-mail address: manuela.petti@uniroma1.it (M. Petti).

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power. Just think of weather, earthquakes, or financial indices, for which we have an immense amount of data, but which never seem to be enough.

A collective work of art

"Works of art create the rules; rules do not create works of art," stated Claude Debussy, the great French composer. Could it not be that the way to diagnose and treat a complex disease is very similar to a work of art, i.e., an activity that requires the "human factor" and not just the "competence" to function? Of course, we must agree on what a "work of art" is, but the main ingredient that interests us here is the collective "creative" aspect of the diagnosis and treatment process. It is obvious that this process can only start from "rules" or "protocols", but it will then necessarily have to depart from them to address this essential "uniqueness" character of a complex disease.

Therefore, the precision physician cannot disregard narrative medicine, which involves complex data (genomics, proteomics, transcriptomics, microbiome, metabolomics, pathomics, radiomics…) as co-protagonists in the construction of the patient's story. To acquire all the necessary information, the data analyst, i.e., the numbers specialist, must also be integrated into this world. We must also consider the other side of the story, and therefore the same data analyst must be involved in the clinical reality that cannot be found in the numbers, becoming an "artist" as well as a number cruncher. A real cross-sharing of knowledge and experience is therefore needed, and this can only be achieved "by involving data scientists directly in the life of hospitals: clinical departments should welcome them, avoiding external offices" [7]. We need the data analyst to visit the wards and the physicians to visit the data analytics labs frequently, and we need both to sit at the same table for a dialogue that considers different points of view.

Achieving this requires new languages of communication that allow the complex dialogue between doctor and data analyst, such as the language of networks [8]. Additionally, it calls for a transformative education from university to postgraduate level, with a focus on ongoing training and discussion, for and between both professionals. This constitutes the real revolution in medicine, a revolution which is undoubtedly mainly scientific and technological, but which requires a radical change in our way of being "doctor" and "data analyst", in its deepest essence. All this implies a challenge with ourselves, an invitation to allow the "other" – the individual with a different expertise – to enter our cognitive path. This represents the most formidable challenge, one that arises from within us, not from an algorithm, regardless of its level of intelligence.

CRediT authorship contribution statement

Marco Filetti: Writing – review & editing, Writing – original draft, Conceptualization. **Manuela Petti:** Writing – review & editing, Conceptualization. **Lorenzo Farina:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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