Strengths and Opportunities of Network Medicine in Cardiovascular Diseases

Giuditta Benincasa, BSc; Raffaele Marfella, MD, PhD; Nunzia Della Mura, BSc; Concetta Schiano, PhD; Claudio Napoli, MD, PhD

Network medicine can advance current medical practice by arising as response to the limitations of a reductionist approach focusing on cardiovascular (CV) diseases as a direct consequence of a single defect. This molecular-bioinformatic approach integrates heterogeneous “omics” data and artificial intelligence to identify a chain of perturbations involving key components of multiple molecular networks that are closely related in the human interactome. The clinical view of the network-based approach is greatly supported by the general law of molecular interconnection governing all biological complex systems. Recent advances in bioinformatics have culminated in numerous quantitative platforms able to identify CV disease modules underlying perturbations of the interactome. This might provide novel insights in CV disease mechanisms as well as putative biomarkers and drug targets. We describe the network-based principles and discuss their application to classifying and treating common CV diseases. We compare the strengths and weaknesses of molecular networks in comparison with the classical current reductionist approach, and remark on the necessity for a two-way approach connecting network medicine with large clinical trials to concretely translate novel insights from bench to bedside.

Key Words: Artificial intelligence; Cardiovascular diseases; Network medicine; Personalized therapy; Precision medicine

Reductionism has been extremely successful in modern medicine by providing enormous advantages in identifying specific abnormalities and targeted treatments. However, it has been accused of oversimplifying our models of cardiovascular (CV) diseases, leading to loss of information about all the molecular determinants and their interactions with the environment, making us not sufficiently ready for precision medicine. Our contemporary viewpoint of CV diseases takes account individual habits, diet, living conditions, comorbidities, and stress leading to heart dysfunction, which cannot be predicted by the investigation of the single parts alone. Now, systems biology can address the dynamic relationship between the single parts of a biological system by shifting the attention to the whole system, to complement reductionism.

After the first proof of concept paper, Barabási coined and popularized the term “network medicine”, which combines systems biology and network science to discover the molecular drivers of human diseases. Network medicine is a holistic approach able to study cells, complex diseases, and social networks in a quantitative manner by focusing on the molecular pathways contributing to onset and progression of CV diseases. This approach reflects the fact that human phenotypes as well as CV traits are driven by complex interactions among a variety of molecular determinants that have to be analyzed at multiple levels, including genome, transcriptome, proteome, epigenome, metabolome, microbiome, exposome, and foodome. Here, we introduce the basic elements of network medicine and emphasize strengths and opportunities in CV diseases with respect to classical analytical methods. Moreover, we introduce the “3P-REVOLUTION”, the acronym of Physicians Perception and Perspective on the care: REnewal from ValidatiOn of aLgorithms by Unifying clinical Trials and Informatics to cOnceive Network medicine. Our message is that a sort of “new French insurrection” is needed to concretely shift from the current reductionism to personalized CV care.

Human Interactome, Biological Networks, Nodes, and Edges

The basic hypothesis of network medicine is that a complex disease results from one or more perturbed molecular networks that are interconnected in the human interactome of disease-related organs (or tissues) and deregulated by genetic and/or environmental changes. Thus, network medicine can use the interactome to explore human disease etiology. We reported some basic principles of network topology analysis to introduce readers to network medicine (see Menche et al for more detailed information). A biological network is a set of points (nodes) that are linked in pairs by lines (edges). Nodes can represent genes, proteins,
and metabolites, whereas edges represent the physical or functional relationships among them, leading to a map that is visualized and analyzed using graph theory (Figure 1). These networks form robust and overlapping molecular circuits able to govern changes in cardiac gene expression in a spatial-temporal manner.

Hypothesis of Disease Network Modules

According to the hypothesis of disease network modules, nodes that are strongly associated with a specific patho-phenotype tend to interact and segregate together in a module (or local subnetwork) (Figure 1). This evidence is supported by different biological phenomena occurring in common CV diseases, such as locus heterogeneity, allelic heterogeneity, and variability of phenotype expression, emphasizing the need for customized treatments. Network medicine offers many modeling approaches to infer relevant disease-gene associations, starting with unbiased analysis of big data (Figure 2, Table 1). This approach has already led to tangible discoveries of putative key nodes and pathways underlying the perturbations of the CV interactome by enlarging the panel of drug targets or biomarkers.

Strengths and Pitfalls of Network Topology Analysis in CV Diseases

Strengths

Network topology analysis has several strengths with respect to the traditional reductionist approach in CV diseases (Table 2). First, the analysis of molecular networks rather than single genes results in a significant reduction of the noise and dimension of data, as well as greater biological interpretability about genotype-phenotype relationships. Importantly, network topology analysis abolishes some limitations in the current human datasets, in which molecular interactions are described without considering the whole context in which they operate. These powerful bioinformatic platforms are able to represent a great amount of heterogeneous big data in the form of relationships in a very simple and intuitive graphic map (Figure 1).

For example, Cytoscape is an open-source software platform.
Figure 2. Flow chart of network analyses. For any specific disease, the pipeline consists of the following steps: (1) reconstruction of the interactome in tissues or cell line of interest; (2) disease gene identification (seed genes) through different sources, including OMIM, GWAS, literature; (3) disease module identification; (4) pathway identification; (5) validation of molecular mechanisms; and (6) prediction. GWAS, genome-wide association studies; OMIM, online Mendelian inheritance in man.

Table 1. Summary of the Main Algorithms Used in Network Medicine

<table>
<thead>
<tr>
<th>Type of network / Algorithm</th>
<th>Principle</th>
<th>Availability</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>PPIs</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>GenePANDA (Gene Prioritizing Approach using Network Distance Analyses)</td>
<td>To identify novel candidate disease genes relying on their relative distance in a functional association network</td>
<td><a href="http://genepanda.tianlab.cn">http://genepanda.tianlab.cn</a></td>
<td>7</td>
</tr>
<tr>
<td>DIAMOnD (Degree-Aware Disease Gene Prioritization)</td>
<td>To identify disease modules around a set of established disease proteins based on the “connectivity significance” instead of “connectivity density”</td>
<td><a href="http://diamond.barabasilab.com/">http://diamond.barabasilab.com/</a></td>
<td>8</td>
</tr>
<tr>
<td>Prodigie (Prioritization Of Disease Genes)</td>
<td>To prioritize genes by implementing a new machine learning strategy based on a set of positive examples (e.g., established disease genes) and unlabeled examples (e.g., candidate genes)</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Regulatory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANDA (Passing Attributes between Networks for Data Assimilation)</td>
<td>To predict regulatory relationships by implementing a message-passing model based on multiple types of information, in order to reconstruct large-scale, disease-specific regulatory networks in yeast as a model</td>
<td><a href="http://www.sourceforge.net/projects/panda-net">http://www.sourceforge.net/projects/panda-net</a></td>
<td>10</td>
</tr>
<tr>
<td>Co-expression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WGCNA (Weighted Correlation Network Analysis)</td>
<td>To identify modules of densely interconnected genes by searching for genes with similar pattern of connectivity in microarray data</td>
<td><a href="http://www.inside-r.org/packages/cran/WGCNA/docs/bicor">http://www.inside-r.org/packages/cran/WGCNA/docs/bicor</a></td>
<td>11</td>
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</table>

Inc-RNA, long non-coding RNA; miRNA, micro-RNA; PPIs, protein-protein interactions.
for visualizing complex networks and integrating these with gene expression data. The most important information arises from networks that are constructed in different time points showing subtle differences of gene expression profiles that really inform us about the molecular processes driving the pathogenesis of CV diseases.\textsuperscript{18,20} Moreover, a huge amount of big data is collected and updated in open-to-public databases, such as GEO, KEGG, DisGeNET, STRING, which integrate information on gene-disease associations from various public repositories and literature.\textsuperscript{3,5} In particular, CardioVINEdb\textsuperscript{21} is a user-friendly independent web interface that can be used with any common web browser. Furthermore, a network-oriented approach can reveal the clinical diseasome to uncover novel mechanistic links between diseases that co-occur more than expected.\textsuperscript{22} This integrated approach has revealed that comorbidities are not causally related to chronic obstructive pulmonary disease but can share genes, proteins and biological pathways as well as risk factors (such as aging, smoking and/or inactivity), which are significantly interlinked in the network.\textsuperscript{23}

### Pitfalls and Opportunities

Disease network discovery derives from the analysis of different data sources, mainly protein-protein interactions (PPIs), that are based on yeast two-hybrid systems and regulatory networks.\textsuperscript{3,5} Therefore, identification of molecular networks is not based on well-established causal relationships, making necessary extensive validation of in silico results by using animal models or human tissue and cell cultures.\textsuperscript{3,5} In particular, researchers can verify if the predicted disease module really exists by perturbing it through pharmacological (e.g., RNA interference) or genetic (CRISPR/Cas9) strategies.\textsuperscript{24} As confirm of computational findings, these perturbations should lead to a change in the phenotype.\textsuperscript{24} In this regard, the use of large animal models, such as dogs, pigs, sheep, and nonhuman primates could be considered before translating basic findings into Phase 1 clinical trials. To date, it is estimated that the human interactome only covers 20% of all potential pairwise interactions.\textsuperscript{4} Because network medicine has its roots in the topology of the interactome, its incompleteness is a great pitfall when basic findings are translated into the clinical arena. Several machine-learning (ML) algorithms are now providing additional PPIs to offer better reliability of results and novel opportunities for diagnostic tools.\textsuperscript{25} Importantly, current knowledge about the detailed 3D structure of proteins is limited leading to several challenges in predicting the outcomes of drug-target interactions, thus unexpected side effects continue to be a problem. This is a frequent cause of failure in clinical trials, where drugs that showed success in vitro fail when used in humans. Remarkably, systems biology has provided novel protein structure networks, treating a protein as a set of residues linked by edges that correspond to the intramolecular interactions.\textsuperscript{26} However, the clinical use of these platforms is challenged by the static view of the proteins that does not reflect the cellular dynamicity. Reliance on the accuracy of a gene ontology (GO) annotation library is another current gap for network medicine. GO terms represent a uniform vocabulary about the function of a particular gene by describing how a gene is regulated at the molecular level and what biological pathways it helps carry out.\textsuperscript{27} To date, researchers largely use GO enrichment methods to analyze high-throughput data and gain insight into the biological significance of alterations in gene expression levels. However, GO terms are assigned either by a human curator who performs careful, manual annotation or by computational approaches that use the basis of manual annotation to infer which terms would properly describe uncharted

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Pitfalls</th>
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<tr>
<td>Feasible visual representations</td>
<td>Absence of translation from animal models to Phase 1 clinical trials</td>
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<tr>
<td>Intuitive visual representations make crucial CV nodes or modules</td>
<td>In silico predicted disease networks should be validated in larger</td>
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<tr>
<td>immediately displayed (e.g., Cytoscape)</td>
<td>cohorts of CV patients</td>
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<tr>
<td>Free online database</td>
<td>Incompleteness of the interactome</td>
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<tr>
<td>CardioVINEdb is a user-friendly platform containing a large set of CV</td>
<td>Global interconnections among the nodes are still not totally known,</td>
</tr>
<tr>
<td>molecular interactions arising from different sources</td>
<td>leading to a gap in identification of disease modules</td>
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<td>Novel candidate gene</td>
<td>Limited knowledge of 3D protein structure</td>
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<tr>
<td>Network-based analysis has successfully predicted novel CV disease genes</td>
<td>The 3D protein structure is not available for the majority of human</td>
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<tr>
<td>Network robustness</td>
<td>proteins, leading to challenges in prediction of outcomes in drug-target</td>
</tr>
<tr>
<td>The network diameter measure can predict the behavior of a complex</td>
<td>interactions</td>
</tr>
<tr>
<td>biological system vs. perturbations</td>
<td>Reliance on the accuracy of GO datasets</td>
</tr>
<tr>
<td>Molecular diseasome</td>
<td>GO annotation is both manual and computational-based and, thus it is</td>
</tr>
<tr>
<td>The molecular diseasome is the representation of diseases that are</td>
<td>continuously evolving and affected by several bias</td>
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<td>linked when they share associated genes or interaction between proteins</td>
<td>Low accuracy of “seed genes” selection</td>
</tr>
<tr>
<td>Clinical diseasome</td>
<td>Most of the complex diseases do not have associated candidate genes</td>
</tr>
<tr>
<td>The clinical diseasome is a global map representing the interdependence</td>
<td>Necessity of dynamic network</td>
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<td>among distinct human diseases when they co-occur more than expected at</td>
<td>Network maps are static whereas the biological networks that</td>
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<tr>
<td>random</td>
<td>represent are dynamic. Dynamic Bayesian algorithms may offer novel</td>
</tr>
<tr>
<td>Optimizing future drug discovery/drug repurposing</td>
<td>opportunities but need further adjustments</td>
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<tr>
<td>Identification of network-based targets may aid in developing novel</td>
<td>Lack of standardized protocols</td>
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<tr>
<td>drugs or repositioning approved drugs</td>
<td>There are no guidelines on experimental standard procedures and</td>
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<td>quality control programs</td>
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CV, cardiovascular; GO, gene ontology.
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Biological findings that are difficult to reproduce under different conditions.

Why Is It Important to Study the Role of PPIs in CV Diseases?

A large list of aberrant protein connectivity has already been reported by reductionist studies. One of the most representative examples of disease heterogeneity derives from inherited hypertrophic cardiomyopathy (HCM). This reality reflects how the reductionist strategies lack in clarifying the dynamic and adaptive features of the genome in the larger context of individual genotype-phenotype relationships. As emphasized by Maron et al., HCM represents a useful example for cardiologists to understand how the reductionism approach has strongly limited a heterogeneous CV disease to sarcomere gene mutations whereas network medicine may explain this disease in its global dimension. By using network-oriented analyses, we

gene products. Thus, GO and its annotations are continuously evolving and affected by a strong bias that may alter interpretation and reproducibility of basic findings over time. As a consequence, specificity of a PPI pathway that regulates a particular cardiac endophenotype (e.g., hypertrophy, fibrosis, apoptosis) strongly hinges on the accuracy of the GO assignment. Some criticisms also derive from the selection of the “seed genes” based on genome-wide association studies (GWAS) that are unable to demonstrate the causal effect in the genotype-phenotype relationship. Another pitfall regards the static character of some bioinformatic tools that are not able to accurately predict the dynamic flow of perturbation through biological networks. In this regard, Bayesian networks are bioinformatic platforms providing dynamic models based on measures of specific variables in different series of samples and CV diseases. Of note, the absence of guidelines/recommendations for biospecimen sources, storage modality and data collection, as well as quality control programs, results in

Figure 3. Deep phenotyping for precision medicine and personalized therapy of cardiovascular (CV) diseases. Established biobanks, such as All of Us Biobank (as part of President Obama’s Precision Medicine Initiative (PMI), https://allofus.nih.gov/), EmCABIOPAN, and UK BIOBANK, as well as consortia represent a great source of heterogeneous information about the heart and its health/disease state (A). For example, tissue biopsy and in particular liquid biopsy are tools to obtain genetic, epigenetic, metabolic, and proteomic data by using omics platforms. Imaging, lifestyle, dietary habits, heart measures, sociodemographic data and electronic health records (EHR) can complement big data (A), providing a “deep phenotyping” strategy (B) able to dissect the network of knowledge in each layer of information at the individual level. This has 2 main clinical implications in CV diseases: personalized therapy (C), in which network-oriented biomarkers may aid in stratifying the risk of CV events and treat patients with customized drugs and precision medicine (D), for which network-oriented biomarkers, phenomapping, and machine learning may be useful to prevent, diagnose and monitor CV patients.
can show how genes interact with each other and unveil novel PPIs through known CV disease genes in the human interactome.33–35

Strengths and Opportunities of Network Medicine in CV Diseases

Precision Medicine and “Phenomapping”

The need for personalized therapy in CV diseases arises from the high clinical heterogeneity characterizing CV patients. A multi-omics panel of network biomarkers may improve traditional population-based risk prediction algorithms (e.g., Framingham risk score) in order to identify high-risk subjects as well as patients with different diagnosis, prognosis, and response to specific drug treatments.38 The current reductionist approach has been somewhat successful and responsible for the most of the drugs currently used in common CV diseases.1,39 One of the main goals of network medicine is to provide biomarkers able to identify specific groups of patients that will benefit from a given therapeutic strategy rather than another avoiding side effects. Collections of biological materials (biobanks) and electronic health records (EHR) for each subject of large study population are becoming indispensable tools to really investigate causal molecular pathways associated with a CV trait.38 For example, large cohort studies (e.g., FHS) and human biobanks (e.g., UK, All of Us, and EmCAB) have provided a great amount of molecular/phenotypic data and biospecimens (blood samples, saliva, urine, tissue samples, genetic material), which are precious resources for translating experimental findings into the clinical setting (Figure 3A).38 Several challenges in network medicine also arise from the implementation of biobanks that generally lack population-specific information, such as genomic background. However, it should be also noted that particular nutrition habits can alter individual epigenetic profiles, making data not extendible to worldwide populations. By using the strategy of “deep molecular phenotyping”, network medicine aims to study a CV patient at each level of knowledge, including genetics, transcriptomics, proteomics, metabolomics, and epigenomics, as well as lifestyle habits (e.g., foodomics) and clinical information (Figure 3B).

As a result, it may be possible to build a “knowledge network” at the individual level, providing a map of the aberrant molecular signaling pathways interlinked with clinical features suggesting novel useful biomarkers for CV precision medicine (Figure 3C). Moreover, it is necessary to say that network medicine does not require the interactome per se; indeed, there are examples of using network medicine to unravel clinical phenotypes.38 Moreover, ML algorithms, such as neural networks and decision tree analysis, have been used to test their putative useful role in assisting diagnosis and clinical decision-making in CV diseases.39,41

Personalized Therapy

The traditional reductionism to drug development focuses on the “one-size-fits-all” approach to patient care that uses prevention strategy or treatment arising from observation of the mean general population.1 In contrast, CV personalized medicine focuses on the identification of “omics” biomarkers for risk prevention and prediction of therapeutic response (Figure 3D). How could network medicine improve CV personalized therapy? Because network medicine can reveal crucial molecular interconnections, it can be used to improve the discovery of novel drugs and molecular targets, as well as in silico drug repurposing.3 Experimental studies have investigated network-based approach to novel drug-target identification and drug repurposing useful for primary prevention and treatment of coronary heart disease. Recently, Lempiäinen et al.42 constructed a co-expression network by integrating GWAS with PPI datasets, revealing novel targets for the current cardiometabolic drugs, including several kinase enzymes and GPCR genes for which drugs already existed, providing new opportunities for CHD treatment. To date, none of network-derived biomarkers, drug targets, or risk prediction models has been implemented in CV clinical care. Actually, network medicine is still labeled as basic research, leading to a real bottleneck effect (Figure 4). The main challenge is to translate basic findings into the CV clinical setting; thus, meta-analysis of large prospective clinical trials is needed (Figure 4). Moreover, it should be recognized that there are other approaches currently being used to identify novel therapeutic targets, such as the “druggable genome”, that have already provided an important contribution to the concept of personalized medicine in CV research.43

“Foodome” Project: Soil for Epigenetics

The impact of dietary habits on medicine (the “foodome”) plays a significant role in quality of life, health and longevity. The term “foodome” refers to a collection of all chemical compounds present in an investigated food sample at a given time, including taste, smell, appearance, texture, and nutritional value. Moreover, large-scale computing and artificial intelligence (AI) have led to food ingredient databases that provide rich details on food contents at the chemical level as well as food trade databases that help to map food production and supply infrastructure. Network medicine is now focusing on the integration of this information to uncover new insights about the relationship between specific food chemicals and consumption behaviors, linking this to health and disease outcomes. Interestingly, the ongoing “Foodome” project (https://www.barabasilab.com/projects) aims to use AI to map, for any given food, its form, function, production, distribution, marketing, science, policy, history, and culture, as well as the connections among all these aspects. This human-ML approach may be useful to analyze foods preferentially consumed by each individual, providing important information about lifestyle, which is one of the most important risk factor for CV diseases.

A metabolomics platform profiled more than 40 foods, including meat, poultry, grains, fruits and vegetables to map food-derived compounds.44 The “food metabolome” is a field largely unexploited but with a great impact on the discovery of novel dietary biomarkers that could reveal hidden molecular networks linking food and health/disease states and then useful indicators of dietary exposures with a high level of precision. It is known that a balanced diet can help to prevent or treat CV risk factors, but how does food affect our health? Food components and their metabolites are emerging as key regulators of epigenetic-sensitive mechanisms, which in turn are linked to CV diseases.45 Several bioactive food compounds, such as resveratrol (RES), are involved in cardioprotection by modifying chromatin structure.46 RES, also known as an epigenetic-based drug (epidrug), is the most investigated plant secondary metabolite in the foodome era, for which several lines of
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than mechanistic findings, AI may provide potent platforms that improve prevention, diagnosis, prognosis and drug response in this field.\textsuperscript{50,51} In the Multi-Ethnic Study of Atherosclerosis (MESA) clinical trial, an integrated ML/deep phenotyping approach was tested to predict 6 CV outcomes in 6,814 asymptomatic subjects over 12 years of follow-up.\textsuperscript{52} By results, this ML platform showed high accuracy in predicting CV diseases; however, a deeper level of validation should be performed to translate these predictive models into clinical practice.

Remarkably, AI is influencing the CV imaging diagnosis of subjects with suspected cardiomyopathies, with huge improvements at different levels ranging from appropriate patient selection, to image acquisition, post-processing and data extrapolation.\textsuperscript{53} Furthermore, by combining AI and cardiac computed tomography angiography data, a novel biomarker named the Fat Attenuation Index (FAITM) has been established.\textsuperscript{54} In detail, FAITM is a measure of adipocyte lipid content and size in the perivascular adipose tissue (PVAT) affected by intra-arterial inflammation that is responsive to statins and PCSK9i, suggesting improvements in personal-

Clinical Road Ahead in CV Diseases

Novel Perspectives From AI

AI is opening novel horizons in the network medicine approach to CV diseases. Based on probabilities rather than mechanistic findings, AI may provide potent platforms that improve prevention, diagnosis, prognosis and drug response in this field.\textsuperscript{50,51} In the Multi-Ethnic Study of Atherosclerosis (MESA) clinical trial, an integrated ML/deep phenotyping approach was tested to predict 6 CV outcomes in 6,814 asymptomatic subjects over 12 years of follow-up.\textsuperscript{52} By results, this ML platform showed high accuracy in predicting CV diseases; however, a deeper level of validation should be performed to translate these predictive models into clinical practice.\textsuperscript{52} Remarkably, AI is influencing the CV imaging diagnosis of subjects with suspected cardiomyopathies, with huge improvements at different levels ranging from appropriate patient selection, to image acquisition, post-processing and data extrapolation.\textsuperscript{53} Furthermore, by combining AI and cardiac computed tomography angiography data, a novel biomarker named the Fat Attenuation Index (FAITM) has been established.\textsuperscript{54} In detail, FAITM is a measure of adipocyte lipid content and size in the perivascular adipose tissue (PVAT) affected by intra-arterial inflammation that is responsive to statins and PCSK9i, suggesting improvements in personal-

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ized treatment.\textsuperscript{54} Despite current limitations in their clinical use, these efforts are of crucial relevance because a total knowledge of molecular interactions is very difficult to realize.

3P-REVOLUTION Challenge

Network medicine offers platforms that systematically explore the molecular complexity of a CV disease by identifying modules and pathways as well as the molecular/clinical relationships between distinct pathophenotypes.\textsuperscript{3,32,55} Of course, progress in this direction is essential to identify novel candidate genes, the functional role of GWAS SNPs, and epigenetic signatures that may provide useful circulating biomarkers, predictive models and novel drug targets.\textsuperscript{56} Moreover, another challenge comes from the possibility of applying network medicine to clarify the direct mechanistic link between transgenerational effects and CV diseases by studying high-risk families and circulating biomarkers at different time points to trace a longitudinal map of the epigenome with crucial clinical implications for primary prevention.\textsuperscript{57,58} Nevertheless, network medicine is a route very hard to walk because it does not represent only a computer-aided experimental setting but a radical new way of operating in modern CV medicine. Indeed, a “bottleneck effect” reflects the current progress in network medicine that is largely limited to basic findings only validated in animal models or human cells (Figure 4). As mentioned, we have introduced the term “3P-REVOLUTION”, which tries to emphasize the synergy of 3 components to really reach precision medicine of CV diseases, including physician evaluation and experience, bioinformatic tools, and clinical validation. Indeed, network-derived biomarkers and predictive computomic models should be investigated in randomized long-term clinical trials to translate the basic discoveries from bench to CV bedside (Figure 4). Despite meaningful advance in clinical research, physicians’ perception and perspective on care again play a huge role in modern CV medicine. We would emphasize this point because this era of AI is a double-edged sword that may build an aseptic clinical reality. How physicians and patients will feel about using and trusting these advanced applications is an aspect that should not be overlooked. A recent published survey reported several concerns about the use of AI from pathologists, especially about the limited presence of digital platforms in many centers and the possibility of errors leading to medico-legal responsibility, suggesting that these will require further in-depth validation before effective implementation in daily clinical practice.\textsuperscript{56} Moreover, we note that several concerns arise from the “diffusion” of network-derived drugs and ML predictive models (Figure 4). Indeed, interactome-based therapy and ML tools might be available for a small number of CV diseases and relegated to universities and excellence centers rather than to wide diffusion to hospitals and home care (Figure 4). These criticisms arise from multiple and difficult ongoing challenges, including costs, time, and the necessity to educate both patients and physicians to accept and use these innovative strategies. Despite its great potential, it should be noted that AI cannot replace the relationship between physicians and their patients. Indeed, traditional fidelity in the physician-patient relationship remains the crucial “hub” of the history of medicine and represents an additional therapeutic tool that none of most advanced technological systems will ever be able to replace. Now there is no enough information to claim that this approach would be better than reductionism. The next step to implement the concept of 3P-REVOLUTION is make to use of several “European infrastructure development projects” (https://www.ecrin.org/activities/projects), for the successful exploitation of integrated omics data to reach personalized medicine in CV diseases. The challenges are to demonstrate the potential and benefits of network medicine for identifying new basic knowledge, facilitate multinational trials and decision making by linking relevant big data repositories while ensuring full compliance with data protection legislation and ethical principles.

Contributors

C.N. and G.B. contributed to the conception and design of the work. G.B., N.D.M. and C.S. researched the data in the literature and wrote the manuscript. C.N. and R.M. provided insights from their experience in CV diseases. C.N. and R.M. supervised and reviewed the final version of the manuscript.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

References


