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A multifaceted 'omics' approach for addressing the challenge of antimicrobial resistance

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ABSTRACT The inappropriate use of antibiotics has severe global health and economic consequences, including the emergence of antibiotic-resistant bacteria. A major driver of antibiotic misuse is the inability to accurately distinguish between bacterial and viral infections based on currently available diagnostic solutions. A multifaceted 'omics' approach that integrates personalized patient data such as genetic predisposition to infections (genomics), natural microbiota composition and immune response to infection (proteomics and transcriptomics) together with comprehensive pathogen profiling has the potential to help physicians improve their antimicrobial prescribing practices. In this respect, the EU has funded a multidisciplinary project (TAILORED-Treatment) that will develop novel omics-based personalized treatment schemes that have the potential to reduce antibiotic consumption, and help limiting the spread of antibiotic resistance.

The antibiotic-resistance crisis

The treatment of infectious disease using antibiotics has been one of the most important advances in modern healthcare, saving millions of lives since their discovery and widespread use. Despite their immense contribution to global healthcare, the CDC recently reported that 'up to 50% of all the antibiotics prescribed for people are not needed or are not optimally effective as prescribed' [1]. Antibiotic overuse typically stems from prescribing these drugs to treat nonbacterial diseases (mostly viral infections) for which they are ineffective. For example, in the USA alone, over 60 million annual cases of viral influenza are prescribed unnecessary antibiotic therapy [2]. Antibiotic misuse has severe health and economic outcomes (Figure 1). Overprescription of antibiotics may cause preventable adverse events such as allergic reactions, intestinal yeast infection and antibiotic-associated diarrhea [3]. These preventable adverse events may impact patient care and result in lengthy hospitalization. In fact, antibiotics are the most common cause of emergency department visits for adverse events in children under the age of 18 years [1]. Conversely, delayed or no antibiotic treatment in cases of bacterial disease is also common (24–40% of all bacterial infections) [4–7]. While this may reduce the risk of antibiotic-related adverse events, such practices can lead to disease-related complications resulting in increased rates of morbidity and mortality [8–10].

KEYWORDS

- antibiotic resistance
- bioinformatics • genomics
- mass spectrometry
- microbiota • proteomics
- transcriptomics

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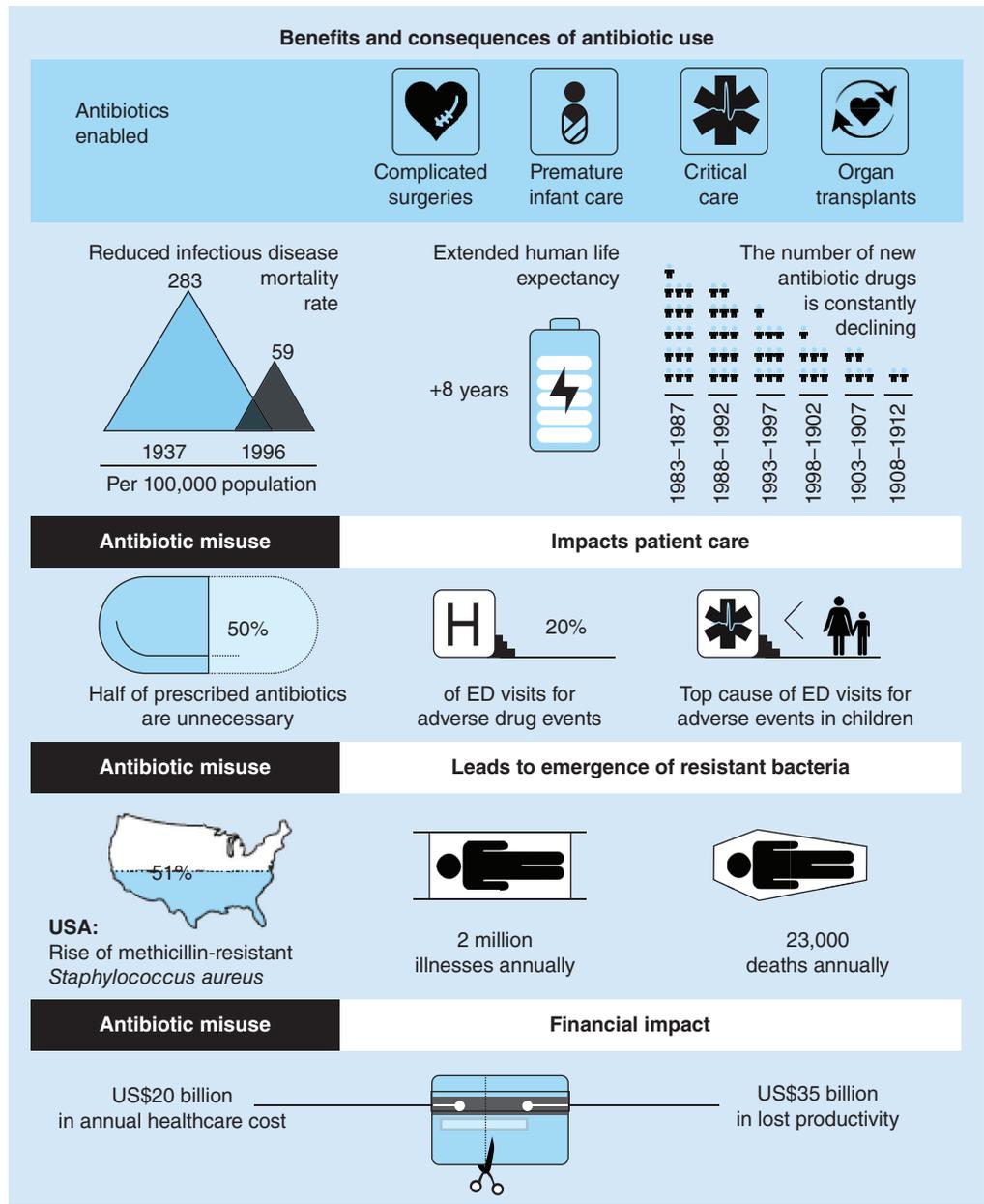


Figure 1. Despite the immense contribution of antibiotics to global healthcare, antibiotic misuse has severe health and economic consequences.

ED: Emergency department.

Data taken from [1,11-13].

One of the most alarming consequences of antibiotic overuse is the emergence and spread of multidrug-resistant bacteria. Resistance of microbial pathogens to antibiotics is increasing worldwide at an accelerating rate [1-2,14-15], with a concomitant increase in morbidity and mortality associated with infections caused by antibiotic-resistant pathogens [1]. At least 2 million people are infected with antibiotic-resistant bacteria each year in the USA alone,

and at least 23,000 people die as a direct result of these infections [1]. In the EU, an estimated 400,000 patients present with resistant bacterial strains each year, of which 25,000 patients die [16]. Consequently, the WHO has warned that therapeutic coverage will be insufficient within 10 years, putting the world at risk of entering a 'postantibiotic era', in which antibiotics will no longer be effective against infectious diseases [17]. The CDC considers this

phenomenon 'one of the world's most pressing health problems in the 21st century' [2,18].

The diagnostic gap

Antibiotic overuse in hospitals and outpatient settings contributes significantly to the rising prevalence of antibiotic resistance [2,11,14]. At the heart of this problem is the challenge of accurately distinguishing between bacterial infections (which warrant antibiotic therapy) and viral infections (for which antibiotic treatment is generally not required). This diagnostic gap is driven by the inability of current diagnostic tools to provide rapid and accurate information regarding the etiological basis of an infection.

- **Technical limitations of current diagnostics**

Conventional diagnostic approaches depend on the cultivation of infectious agents and subsequent testing for antibiotic sensitivity and resistance. This process requires lengthy cultivation periods (days) and is not applicable for certain bacterial infections, or for most viral infections. Nucleic acid amplification-based tests (NAAT) for direct pathogen detection are showing considerable promise. Their advantages include high sensitivity and the simultaneous detection of multiple pathogens. Consequently, these tests are increasingly used in hospital and laboratory settings [19,20]. However, NAAT protocols exhibit varying degrees of sensitivity and specificity when identifying specific pathogens and antibiotic resistance traits. In addition, NAAT diagnostic technologies usually require direct sampling of the pathogen. Such sampling is often not easily feasible if the infection site is not easily accessible (e.g., sinusitis, middle-ear infection and bronchitis) or the site of infection is unknown (e.g., fever of unknown origin).

- **Reduced clinical utility due to colonizers**

Moreover, currently available diagnostic approaches often suffer from reduced clinical utility because they do not distinguish between pathogenic strains of microorganisms and potential colonizers, which can be present as part of the natural microbiota without causing an infection [21–24]. For example, Rhedin and colleagues recently tested the clinical utility of quantitative PCR (qPCR) for common viruses in acute respiratory illness [24]. The authors concluded that qPCR detection of several respiratory viruses including rhinovirus, enterovirus and

coronavirus should be interpreted with caution due to high detection rates in asymptomatic children. Other studies reached similar conclusions after analyzing the detection rates of different bacterial strains in asymptomatic patients [25,26].

The described limitations of current diagnostic procedures lead physicians to either overprescribe ('just-in-case') or underprescribe ('watchful waiting') antibiotics, both of which can adversely impact patient care and health economics. Therefore, there is a clear need for novel solutions that will empower physicians to make early, evidence-based antibiotic treatment decisions, in order to improve patient care, reduce adverse events and limit the spread of antimicrobial resistance.

A multifaceted 'omics' approach for reducing antibiotic resistance

Meeting the challenges of antibiotic resistance requires adopting an integrative approach that expands the antimicrobial arsenal on the one hand and reduces antibiotic consumption on the other [11,27–28]. New antibiotic drugs are desired, but will likely provide only a temporary solution in light of the inherent ability of microbes to develop new resistances by a variety of physiological mechanisms, including the exchange of transferable genetic elements, uptake of DNA by transformation and transduction and DNA mutation. Moreover, only a handful of new antibiotics are likely to reach the market in the near future due to the 'broken pipeline' associated with their development [29]. Several factors have undermined the economic incentives for the development of new antibiotics in recent years, including: the significant financial commitment required for developing new drugs (including research, development and regulatory approval costs); the use of antibiotics for brief periods of time, usually on a 'need-only' basis; the restricted use of new and costlier antibiotics for more severe cases as a 'last-resort' option; and the higher economic incentives for developing medications for the management of chronic conditions, which originate from their continuous consumption for long periods of time (months or years). Recently, in trying to fix this 'broken pipeline', several governmental initiatives in the USA and Europe have been launched, in order to provide financial incentives for the development of new, innovative antibiotic drugs [11,30–31].

Complementary to the development of new drugs is the need for a significant reduction

in antibiotic consumption. This goal may be achieved by increasing public awareness of antibiotic misuse and its consequences, as well as by adopting new diagnostic approaches to bridge the current diagnostic gap. However, though recent antimicrobial stewardship programs have gained some success in reducing overall antibiotic consumption in several countries across the globe [32], further improvements in global antibiotic prescribing practices are still required [1,33].

New technologies are constantly emerging, providing the scientific and medical communities with powerful tools to improve the diagnosis of infectious diseases. Advances in the analysis of pathogens and the host immune response to infection in a broad and sensitive manner have led to a deeper understanding of complex host–pathogen–treatment interactions [28]. Technologies such as next-generation sequencing provide snapshots of the patient's entire transcriptome in response to an infection or treatment, as well as enable the genetic analysis of the patient's natural microbiota (microbiome). These technologies also facilitate the search for novel genetic variation markers (single nucleotide polymorphisms [SNPs]) that may predispose individuals to specific infections and disease progression. Most importantly, advances in bioinformatics algorithms and 'big-data' analysis enable the integration of clinically relevant information such as host genetics, microbiota, response to treatment and data on the disease-causing agent. Mining this integrated data to generate treatment algorithms, coupled with the development of intuitive web-based interfaces, will be a major step forward in the management of infectious disease patients. Not least in the ongoing battle against antimicrobial resistance.

The TAILORED-Treatment research program

The EU is investing public funds in a range of multidisciplinary scientific programs that harness recent technological advances for addressing the challenges of antimicrobial resistance. One of the recently funded projects is the 4-year 'TAILORED-Treatment' research program, which focuses on the diagnosis of infectious disease etiologies for guiding antibiotic treatment in patients with respiratory tract infections and/or sepsis [34]. The project combines state-of-the-art omics-based techniques and data with multivariate analysis methods and newly developed

bioinformatics software with the goal of translating novel host-pathogen insights into treatment decision support algorithms. At the heart of the project is a large multicenter prospective clinical study enrolling 1200 adult and pediatric patients, where patient and microbe-related information is being collected (Figure 2). The data are being investigated for significant associations between multiple biological and clinical parameters (Figure 3). New scientific discoveries generated by such omics-based approach will serve as a foundation for novel diagnostic solutions and for new web-based decision support systems for the physician of the future. The 'omics' approach of the TAILORED-Treatment program for personalizing antimicrobial treatment is further described below.

• Host genomic analysis

SNPs are the most common type of genetic variation found among individuals, with approximately 10 million SNPs in the human genome [36]. Each SNP represents a difference in a single nucleotide at a single position in the genome, which can occur in noncoding, regulatory or coding regions, and thus can affect the function of specific genes. Thousands of SNPs have already been shown to have a robust association with hundreds of different traits and diseases [37]. Importantly, recent genome-wide studies have reported novel associations between common polymorphisms and susceptibility to several major infectious diseases of humans [38]. For example, genetic polymorphisms were implicated in the susceptibility, severity and outcome of meningococcal disease [39,40]; polymorphisms in the Toll-like receptor 2 and the anti-infective cytokine IL-17A gene increase the risk of serious Gram-positive infections [41], and a specific set of host genetic polymorphisms was recently suggested to be the predominant determinant for *Staphylococcus aureus* persistent nasal carriage [42].

Genetic polymorphism can also determine the response to treatment [36]. Multiple genome-wide association studies in different populations have reported strong associations between IL-28B polymorphism and the response to hepatitis C virus treatment [43–46]. Other studies have found associations between genetic variation in the HLA-B region and hypersensitivity reactions to HIV therapy [47–49], and suggested genotypic testing as a simple predictive screening tool for hypersensitivity reactions to specific anti-HIV drugs [50,51]. Host genome analysis is being performed in infectious

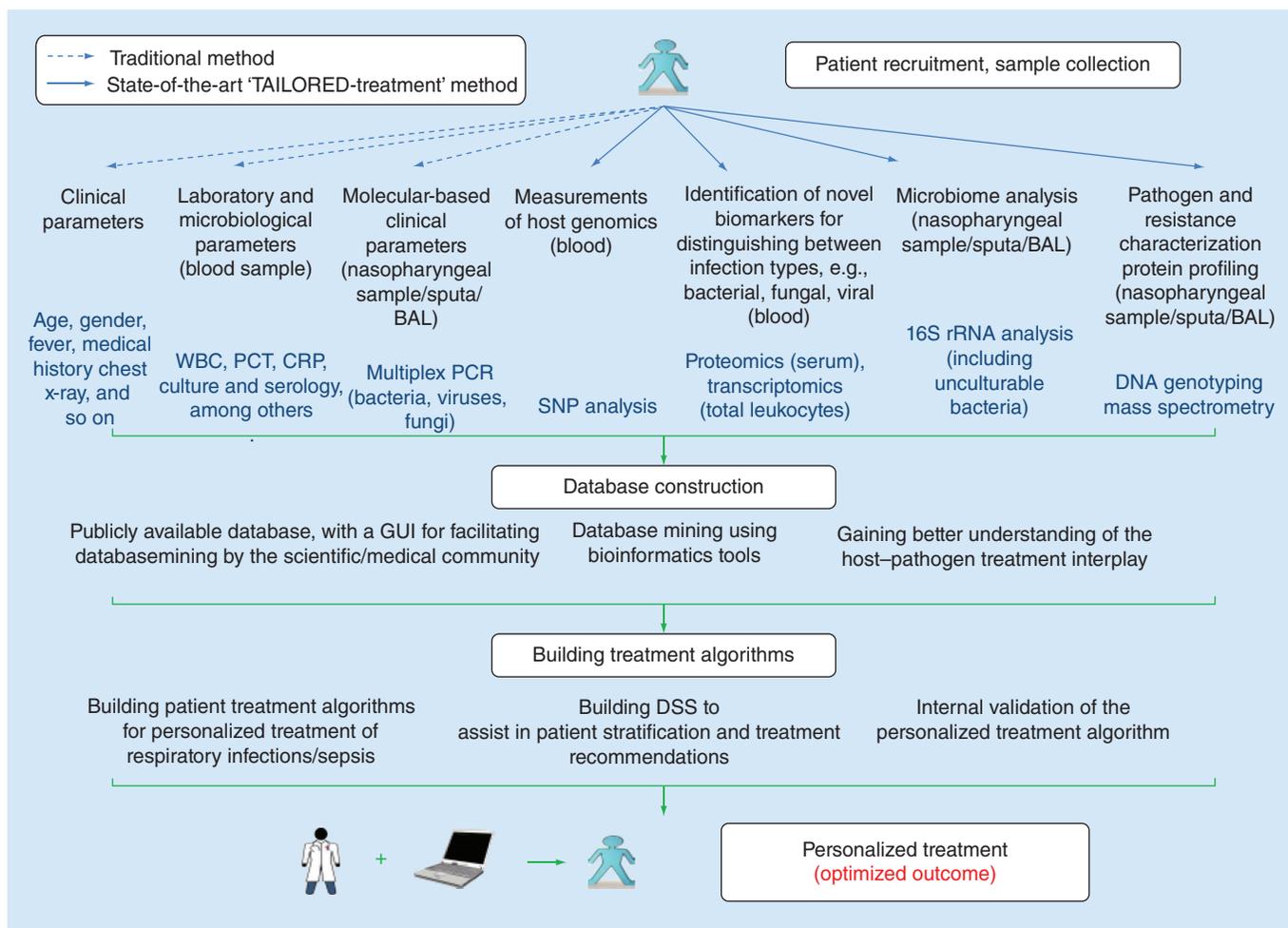


Figure 2. Multifaceted approach adopted by the TAILORED-Treatment consortium to help personalize antimicrobial prescribing practices to individual patients. Traditional and state-of-the-art omics-based techniques are being utilized to perform comprehensive patient and pathogen analyses that combine clinical data, proteomics, transcriptomics, microbiome analysis, genetics and bioinformatics. The collected data are used to identify novel host-pathogen-treatment dynamics and generate a web-based predictive treatment algorithm for use by physicians.

BAL: Bronchoalveolar lavage; CRP: C-reactive protein; DSS: Decision support systems; GUI: Graphical user interface; PCT: Procalcitonin; SNP: Single nucleotide polymorphism; WBC: White blood cell.

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disease patients in order to identify novel SNPs potentially associated with predisposition to specific types of infections, disease progression and response to treatment (pharmacogenomics).

• Host transcriptomic & proteomic response to infection

Fashioned by evolution, our immune system has evolved for millions of years to distinguish between bacterial, fungal and viral pathogens. Deciphering the host response to these different types of infections can reveal valuable diagnostic biomarkers for guiding clinical treatment decisions. Importantly, this approach addresses

several challenges posed by current microbiological tests by enabling: diagnosis even in cases of not easily accessible or unknown infection sites (e.g., lower respiratory tract infection, fever without a known source in children); rapid measurement of soluble host proteins (within minutes) on hospital-deployed automated immunoassay machines and point-of-care devices; and diagnosis that is not affected by the presence of potential colonizers that comprise our natural microbiota. Based on this, a paradigm shift for diagnosing infections has been gaining ground in recent years: instead of targeting potential infectious pathogens, diagnosis

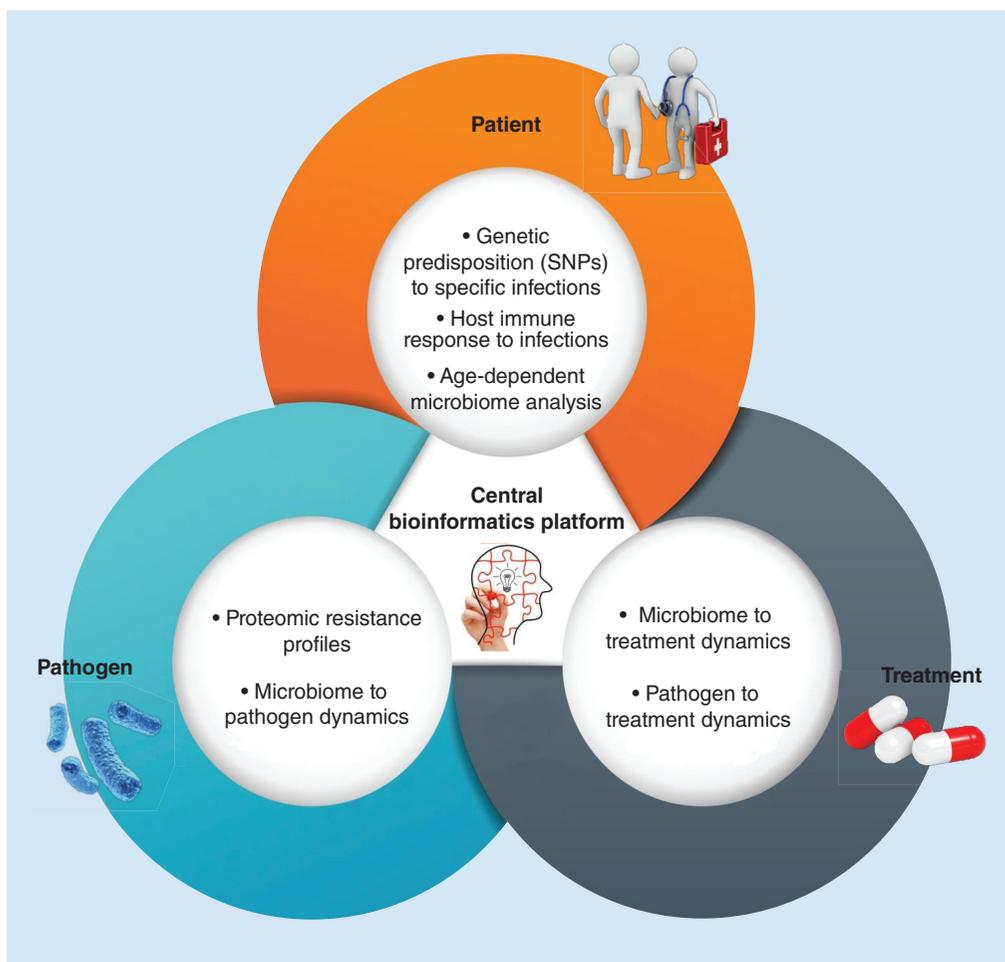


Figure 3. New insights to be gained using a multifaceted omics-based approach for studying patient–pathogen–treatment interactions. Omics-based surveys of the host transcriptome, proteome, genome and microbiome within a large cohort of patients will generate a substantial amount of novel data. The newly collected data are stored and mined using a dedicated bioinformatics platform, enabling efficient statistical analysis and the identification of significant associations between the different data sets.

SNP: Single nucleotide polymorphism.

could be based on the host immune response to infection [52,53].

Traditional high-throughput RNA measurements have identified promising novel host-RNA biomarkers [52–58]. The pioneering works of Ramilo [57] and Zaas [56] have demonstrated, in small cohorts of human subjects, the potential of gene-expression patterns to discriminate between patients with different etiologies. However, applying host RNA-based signatures in the clinical setting requires discovery and validation of RNA signatures in large cohorts of human patients presenting with a wide range of pathogens. Additionally, most RNA biomarker discovery efforts have thus far been focused on gene level exploration (i.e., mRNA) [54–57],

although up to 70% of the human genome is transcribed into RNA that does not serve as templates for proteins [59]. Next-generation sequencing technologies and novel human transcriptome microarrays allow high-throughput, quantitative surveys of the transcriptome, capturing a broader range of gene expression changes in response to external conditions and enabling the detection of novel transcripts including mRNAs, non-coding RNAs and small RNAs [60,61]. Although these technologies were introduced only several years ago, they have already triggered numerous groundbreaking discoveries and ignited a revolution in genomic and transcriptomic science [60,61].

The TAILORED-Treatment project is using biochemical and advanced high-throughput

technologies to screen both the host proteome and host transcriptome in search of novel biomarkers that distinguish between viral, bacterial and fungal infections, both in children and adults. Comprehensive transcriptome analysis is being performed to explore the immune arm of the noncoding RNA, being based on recent evidence that noncoding RNAs may be valuable building blocks of the host response to infection [62]. Machine learning schemes are being used to generate multiparametric signatures combining different biomarkers in order to overcome the challenge of patient-to-patient variability.

- **Microbiota/microbiome analysis**

A microbiome is defined as the collective genomes of various microorganism communities (microbiota) that inhabit and share our body space [63]. This includes the microbiota found in the gut, mouth, nostril and vagina, as well as the microbiota present on the skin [64]. Approximately 90% of the cells in and on the human body are microbial cells, which routinely contribute to tissue and organ function [63]. The microbiota composition may correlate with an individual's genotype, diet and overall health status. For example, a 'Western' diet comprising high intakes of protein and fat may generate a different gut microbiota/microbiome when compared with an agrarian plant-rich diet [65]. Thus, studying the different characteristics of microbial communities can provide valuable information on human health and disease predisposition [66,67]. In 2007, the NIH launched the Human Microbiome Project, aimed at creating a reference catalog of microbial DNA for building data sets that may provide insight into how an individual's microbiome signature relates to his/her health and disease status [68]. Thus far, Human Microbiome Project research centers have generated over 14 terabytes of new microbiome sequence data, which are available to the global community of microbiologists [69]. Using these new data, studies have associated the human microbiome with a wide range of pathologies, including those of the gastrointestinal tract, respiratory tract, skin and nervous system [66,67]. Recent reports also indicate that the microbiota composition is a major predictive factor of the type and robustness of the host mucosal immune response [70]. Finally, it has been shown that antibiotic treatment

affects both the disease-causing agent and the microbial ecology, thereby affecting host metabolism [71].

In light of the emerging importance of the microbiota/microbiome in health and disease, and the new technologies that enable its broad analysis, a patient's microbiota/microbiome should be considered a critical component when developing personalized antimicrobial treatment schemes. The TAILORED-Treatment project is mapping the respiratory (nasal) microbiota in children and adults suffering from respiratory or sepsis-related disease in order to discover new host-microbe interactions related to age, gender and treatment. Age-related differences in the human microbiome have already been described [72]. Microbiota maps are also being integrated with relevant clinical data in order to assess how a patient's natural microbiota affects pathogenicity levels, disease progression and overall health outcome.

- **Rapid profiling of pathogens**

The TAILORED-Treatment program is also seeking to develop and improve techniques for rapid pathogen identification and antimicrobial resistance profiling. Increasingly, microbiology laboratories are using mass spectrometry to study microbial pathogens and to identify antibiotic resistances. However, validation of this technique on a diverse spectrum of clinical samples is a prerequisite for its widespread use. Moreover, such procedures currently require that infectious microorganisms first be cultured, which imposes significant time constraints on patient treatment regimens. The development and integration of a mass spectrometry-based method that can rapidly identify and characterize bacterial isolates directly from clinical specimens (i.e., without the prior cultivation of the infectious microorganisms) would enable 'real-time' informed decisions to be made regarding whether to administer antibiotic therapy to a patient, and which class of antibiotics to use.

A mass spectrometry proteomics-based approach is being further developed in order to reduce the time from sample collection to full pathogen profiling, as another step toward the adoption of this technique in different clinical settings. Such diagnostic tools will provide answers to physicians within 5 h from the time of sample collection, compared with approximately

48 h using current gold-standard procedures for identifying pathogens and their antibiotic resistance. To achieve this, technologies such as lipid-based protein immobilization are being utilized, whereby intact bacterial cells are bound, via membrane–gold interactions, within a flow cell [73]. The bound cells are subjected to enzymatic digestion for the generation of peptides, which are subsequently identified, using LC-MS. Following database matching, strain-specific peptides are used for subspecies-level discrimination. This method has been shown to enable reliable typing and identification of closely related strains of the same bacterial species [73,74].

• **Systems level analyses**

Omics-based surveys of the host genome, transcriptome, proteome and microbiome within a large cohort of patients will generate a substantial amount of different types of data. One of the biggest challenges toward gaining new insights into host–pathogen–treatment dynamics is the integrative analysis of different layers of data, required for identifying significant associations between the various data sets. As a first step, classical clustering (e.g., K-means [75] or different kinds of hierarchical clustering) and feature selection algorithms (e.g., Relief or Logo [76]) are required to identify key variables, to weight the importance of these variables as markers and to test the predictive power of these markers. Using these algorithms to analyze diverse data often requires their customization or the development of new software tools that can enable the joint analysis of different types of data (e.g., categorical and numerical variables). The next step is to apply a range of tools to process the integrated data and extract systemic associations. For example, association rule learning is a popular and well-researched method for discovering interesting relations between variables in large databases [77]. Additionally, decision trees (e.g., C4.5 [78]) can provide an intuitive view of the behavior of the data, while functional enrichment tools (e.g., integrating gene ontology annotations) can allow the integration of expert knowledge within the analytical results. More sophisticated dimensionality reduction algorithms (e.g., isometric feature mapping [ISOMAP] [79]) are necessary to enable the modeling of complex manifolds comprising data from different sources, whose behavior would be impossible to reproduce using simpler algorithmic methods. Finally, in

order to simplify the direct and rapid extraction of information the tools described above should be integrated with associated databases in a common framework. The advantages of this combination include the possibility to set up preconfigured pipelines that are targeted to the analysis of different types of data, the reliable definition of costumed sub-data sets and the establishment of target variables, that is, the definition of the question to be answered by the system.

• **Web-based decision support system**

The knowledge gained using omics-based data collection and analysis is being used to develop new personalized treatment algorithms. Such algorithms will help physicians tailor antimicrobial therapies to the specific and evidence-based requirements of children and adults presenting with respiratory infections and sepsis. Personalized treatment algorithms are being integrated into a simple, web-based interface that will be made available to physicians, allowing them to make predictive clinical decisions, including the correct targeting of antibiotic treatment to the actual personal needs of the patient.

Conclusion

The problem of increasing antibiotic resistance is a global phenomenon that is now being appreciated by governments and citizens alike. No single solution is able to avert the continuing dissemination of worldwide multiresistant bacterial strains. Instead, a consolidated and coordinated global effort is required, which includes the development of more rapid and accurate diagnostics for bacterial infections. With this in mind, the TAILORED-Treatment concept takes a step towards the near future, where omics data will be readily available for consultation by physicians and (together with clinical data) will help provide essential information for the rapid and accurate diagnosis of bacterial infections.

Future perspective

Technological advances in the current post-genomic era will continue to generate a wealth of data at both the patient and pathogen levels. This is due to the publication of a growing number of complete genome sequences for a large range of clinically relevant pathogenic microorganisms, as well as the publication of complete human genomes from subjects representing a wide range of ages, gender and races [80]. Novel

desktop-size machines can now rapidly sequence a whole human genome at a cost approaching US\$1000, compared with over US\$2 billion (the cost of the human genome project a decade ago). Sequencing devices are becoming smaller and cheaper, making the dream of using personal genomic and transcriptomic data in routine visits to the doctor's office a tangible reality. Concurrently, the information revolution of recent years has allowed the clinical community to address common practice challenges by sharing tools, information, scientific publications, and experience. Additionally, affordable smartphones are becoming an integral part of medical practice, with a variety of applications that literally bring healthcare to the palm of the clinician's and patient's hands. Real-time monitoring of patient vital signs together with the constant delivery of healthcare information to clinicians empowers patients to control their chronic conditions and maintain their normal daily routine. This approach is expected to be significantly enhanced by the introduction of new wearable health devices, which will increase the variety of vital signs that can be constantly monitored [81]. These technological advancements are expected to facilitate the integration of personalized data into routine clinical care. We envision a future where physicians will use machine learning-based decision support systems, which integrate patient personal data with host and pathogen diagnostic biomarkers (Figure 4), to diagnose and treat patients. Patient diagnosis will combine traditional clinical parameters with omics-based personal data, including: the genetic predisposition to certain types of infections; the response to different classes of drugs; and the dynamics of the microbiota/microbiome in response to treatment. Computerized integration of these data will mean that real-time recommendations can be made regarding the optimal treatment regimen for each patient, as well as a prediction of patient prognosis and health outcome. The challenge for the future will be how to best interpret and efficiently act on this wealth of data. The timely creation of validated algorithms and simplified user interfaces will help establish a new range of 'gold standards' in personalized clinical treatment, ultimately informing and advising both clinicians and patients on the best treatment options available. The extensive use of such multifaceted algorithms for the management of infectious disease patients will not only improve patient



Figure 4. The future of personalized infectious disease therapy. Cloud-based computational platforms will be integrated with patient-based omics information such as genomics, transcriptomics, proteomics, microbiome and drug metabolism kinetics to generate accurate physician-friendly algorithms. Combining accessibility to personal data and algorithms with point-of-care diagnostic tests has the potential to transform the management of infectious disease.

care but also help reduce antibiotic consumption, ultimately limiting the spread of antibiotic resistance.

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EXECUTIVE SUMMARY

The antibiotic resistance crisis

- Despite their immense contribution to human health, up to 50% of all the antibiotics prescribed for people are not needed or are not optimally effective as prescribed.
- One of the most alarming consequences of antibiotic overuse is the emergence and spread of multidrug-resistant bacteria.
- Resistant bacteria infect over 2 million people annually in the USA and over 400,000 people in the EU, resulting in thousands of deaths.
- Antibiotic-resistant infections cost the US healthcare system an estimated US\$20 billion annually, with an additional estimated US\$35 billion in lost productivity.

A diagnostic gap

- Among the factors underlying antibiotic misuse is the challenge of accurately distinguishing between bacterial infections (which warrant antibiotic therapy) and viral infections (for which antibiotic treatment is generally not required).
- This diagnostic gap is driven by the inability of current diagnostic tools to provide rapid and accurate information about the etiology of an infection.
- Reaching a definite diagnosis is complicated by not easily accessible or unknown infection sites, the difficulty to distinguish between pathogenic and commensal bacteria and the prolonged time required to achieve a definitive result.

A multifaceted 'omics' approach for reducing antibiotic resistance

- Meeting the challenges of antibiotic resistance will include the development of new drugs and innovative strategies for improving diagnosis and treatment of infections.
- Gaining deeper understanding of complex host–pathogen treatment interactions through new omics-based technologies offers a unique opportunity for the development of personalized diagnosis and treatment schemes.
- This approach requires adopting an integrative approach to clinical diagnosis and disease prognosis prediction that brings together different disciplines from the medical, computational and life sciences.

The TAILORED-Treatment research program

- The EU recently funded a multidisciplinary research program (TAILORED-Treatment) to improve the understanding of host–pathogen treatment dynamics in respiratory and septic patients.
- The project combines clinical data, proteomics, transcriptomics, microbiome analysis, genetics and bioinformatics to develop novel personalized treatment algorithms.
- These algorithms will be integrated into a web-based decision support system that will be made available to physicians.
- Evidence-based decision support systems will enable faster, better-informed antibiotic treatment decisions, thereby limiting the emergence and spread of antibiotic resistance.

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