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D1.3 Technological Roadmap for diagnostics of CAARTI

VALUE-Dx

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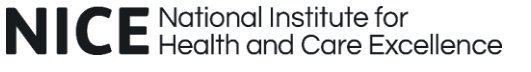
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1. Introduction

The VALUE-Dx project aims to transform clinical practice, improve patient outcomes, and combat antimicrobial resistance (AMR), through the widespread use of clinical and cost-effective innovative diagnostics strategies to achieve more personalized, evidence-based antibiotic prescription and use in community care settings.

To achieve this, we aimed to develop a Technical Roadmap to guide future development and implementation of CA-ARTI point-of-care diagnostics supported by evidence and tools. The Roadmap development was undertaken in close interaction with WP 1.2 User Requirement Specification and was done with the following steps

- Landscape analysis of commercially available and emerging commercial diagnostic tests for respiratory tract infections (RTIs)
- User Requirement Specification and Target Product Profile Development (WP1.2)

2. Approach

2.1. URS/TPP Focus Group

The work undertaken in WP1.3 was started before COVID-19 with an in-person workshop as planned. However, this approach had to be modified due to the restrictions during the pandemic and was largely carried out remotely. To coordinate these tasks a focus group as part of WP1.3 (and WP1.2) was convened which met fortnightly to monthly, depending on upcoming tasks. The membership was chosen to have a balanced representation of the VALUE-Dx project partners and expertise.

Table 1: Members and former members of the URS/TPP Focus Group

Members	**Former Members**
Till Bachmann, University of Edinburgh (Lead) Benjamin Hommel, BioMérieux Herman Goossens, University of Antwerp Suzanne Seme, Abbott Céline Blangy, BioMérieux Celine Roger-Dalbert, Becton-Dickinson Janneke van de Wijgert, UMC Utrecht Jennifer Osborn, FIND John Verrant, Janssen Mical Paul, RAMBAM	Alex Van Belkum, BioMérieux Anders Ros, Abbott Marie-Francoise Gros, BioMérieux

2.2. Landscape of diagnostic tests for respiratory tract infections

We undertook a systematic search between 2019 and 2023 for commercial diagnostic tests for RTIs. As sources we used the list of companies attending the European Congress of

Clinical Microbiology and Infectious Diseases[1], the companies mentioned in the WHO 'Landscape of diagnostics against antibacterial resistance, gaps and priorities'[2], and search hits for "Respiratory" at GenomeWeb[3] and 360Dx[4] web directories. Tests only targeting SARS-CoV-2 were not included. A landscape of the relevant diagnostic tests was developed based on the information retrieved from the website and the product insert of each test and entered in to an Excel based database for VALUE-Dx.

2.2.1. Landscape analysis of commercially available diagnostic tests for RTIs

We included a total of 390 diagnostic tests from 86 companies in the landscape. Of these, we considered almost half (45%, 176/390) suitable for their use at the point of care based on the supplier's information. The main methodology used by the tests was immunoassay (47%, 184/390), followed by PCR (33%, 128/390) and culture (11%, 42/390). Assays based on isothermal amplification only represented 4% of the tests (14/390). Regarding diagnostic targets, 46% (179/390) of the tests aimed for bacterial pathogens, 41% (160/390) for viral pathogens, while only 5% (20/390) were able to co-detect bacteria and viruses, and 8% (31/390) were based on the biomarkers C-reactive protein (CRP) or procalcitonin (PCT). Importantly, 36% (139/390) of the tests took a panel approach and could detect more than one pathogen, and the majority of these (81%, 113/139) required an instrument. The most common result readout method was the instrument displaying the result (35%, 138/390), closely followed by colorimetry (34%, 134/390). Finally, almost half of the included tests required less than 20 minutes to deliver the result (47%, 184/390), while a large proportion of the tests needed between one hour and six hours to provide the result (33%, 130/390). Immunoassays and isothermal amplification had the shortest time-to-result, while cultures required the longest. Out of the 176 tests that are suitable for the POC, most were based on immunoassays (89%, 157/176) but much less on PCR (9%, 15/176) or isothermal amplification (2%, 4/176). Associated to this, most tests gave the result as a colorimetric readout (61%, 108/176), while in only 27% (47/176) the instrument displayed the test outcome. Similarly, most POC tests did not require instrumentation to be performed (61%, 107/176). The most common targets for POC tests were Group A Streptococcus (22%, 39/176) as bacterial pathogen and Influenza (33%, 58/176) and respiratory syncytial virus (RSV) (24%, 43/176) as viral pathogens.

2.2.2. Landscape analysis of commercially emerging diagnostic tests for RTIs

In addition to the overview of commercially available tests, we developed another landscape covering current commercial development of new diagnostic tests for respiratory tract infections. In this case, GenomeWeb and 360Dx were screened as before. In addition, we included participants of the Longitude Prize on AMR targeting RTIs[5]. This search yielded 39 tests, with a high dominance of POC suitable (56%), but instrument-requiring (95%) tests. The most common methods used in these tests were PCR (28%), immunoassays (26%) and isothermal amplification (23%). Despite being able to be categorised in previous methodologies, these emerging tests were based on innovative techniques, including single-cell analysis, microcolony growth, volatile organic

[1] https://www.escmid.org/congress-events/escmid-global/
[2] https://www.who.int/publications/i/item/10665326480
[3] https://www.genomeweb.com/
[4] https://www.360dx.com/
[5] https://amr.longitudeprize.org/teams/

compound detection, photonics, CRISPR and sequencing. Remarkably, 13% of the tests were being developed to differentiate bacterial from viral infections, rather than detecting specific pathogens. We did not include a review of the scientific literature or academic research on technologies which might have a use in the diagnosis of RTIs in the community as this would have been be beyond the scope of this study.

3. Aligning the diagnostics development process

Technology Readiness Levels (TRL) and Product Development Plans (PDP) are key tools for planning and assessing the development of in vitro diagnostic products. To reflect the specific needs for diagnostic test development, we propose a dedicated TRL Scheme which specifies activities, milestones and outputs at each stage. TRLs measure the maturity of a technology on a scale of 9 levels, with higher levels indicating readiness for market uptake. Each level of the TRL scale corresponds to a specific stage in the development of the technology, from the initial concept (TRL 2) to the experimental proof of concept (TRL 3), through to the technology's validation in a controlled environment (TRL 5), and finally to its demonstration in an operational environment (TRL 7) before it is fully mature and launched (TRL 9). Each level of the TRL scale corresponds to a specific stage in the development of the technology, from the initial concept (TRL 2) to the experimental proof of concept (TRL 3), through to the technology's validation in a controlled environment (TRL 5), and finally to its demonstration in an operational environment (TRL 7) before it is fully mature and launched (TRL 9). TRLs create a consistent framework for discussions on technology maturity and are crucial in the EU's Horizon 2020 program, impacting project funding.[6] For diagnostic companies, TRL is key in acquisition decisions, balancing the risks and costs of acquiring early-stage technologies versus more mature ones. Considerations include market demand, regulatory challenges, and alignment with strategic goals to guide investment decisions at each TRL stage.

Beyond the TRL scheme, the diagnostic industry uses Product Development Plans (PDP) in a phased approach that aligns business projects and design controls. It consists of five phases: Phase 0 involves creating a business proposal based on research, opportunities, and strategy. Phase 1 focuses on definition and feasibility, followed by design and verification in Phases 2a and 2b. Phase 3 covers validation, and Phase 4 addresses commercialisation. Reviews occur after each phase (P0R to P4R), with key 'Go/No-Go' decisions made after Phase 1 and Phase 3. The process can still be halted during these stages.

[6] Héder M. From NASA to EU: the evolution of the TRL scale in Public Sector Innovation. The Innovation Journal: The Public Sector Innovation Journal. 2017;Volume 22(2)

4. Roadmap for the development of diagnostic tests for RTIs

We initially intended to undertake the technical roadmapping through a series of in person workshops involving key stakeholders of CA-ARTI diagnostics. This process was kicked off in 2019 through a facilitated[7] roadmapping training workshop involving the VALUE-Dx General Assembly and Executive Board members. Outcomes and outputs from this workshop fed into the revision of the roadmapping strategy due to the COVID-19 pandemic leading to the formation of the VALUE-Dx URS/TPP Focus Group and the landscaping of diagnostic tests, User Requirement Specification and TPP development approach (WP 1.2). For the Roadmap, the Optimal Criteria of the TPPs were considered technically aspirational in 2023 and expert opinion was gathered to inform the likelihood, timeline and approach to achieving these characteristics.

The Kick-Off workshop for the Roadmapping identified on a high level the inappropriate use of antibiotics, the rising rate of AMR, tightening regulation, rising healthcare costs as well as a current lack of awareness of AMR with a long-term desire of the patient to take control over their own health, increasing mobile testing and the advent of microbiome management as drivers for the CA-ARTI diagnostics field.

The participants ranked the trends and drivers for the CA-ARTI landscape with inappropriate antibiotic use leading followed by current health care policies, lack of knowledge on antibiotics use among EU citizens, education of society about bacterial vs viral infections, economic drivers, emerging demand for 'no antibiotic treatment without prior diagnostics', aim to reducing AMR, increasing cost in healthcare, north/south divide in Europe regarding antibiotic resistance, need for public awareness raising on AMR and need for better diagnostics & treatments. As overarching drivers, the participants included health inequalities and climate change. These drivers were considered to be met by a medium to long-term research landscape centred around data science, diagnostics technology, development of new drugs, stewardship, basic science, social science, business planning and policy. Specifically, the participants ranked as top 10 research areas rapid diagnostics tests, educating stakeholders on diagnostic testing and AMR stewardship, large coherent clinical studies, public and doctor education, educating policy makers, translation from academic research to market & improving/facilitating collaborations between academia and industry, comparative effectiveness evidence for POC diagnostics, health technology assessment and regulatory pathways for diagnostics, innovative pricing and reimbursement policies, and real-time epidemiology. Overarching enablers including technologies, capabilities and resources were identified as awareness raising, technological research, surveillance, data exchange, economic models and transnational partnerships and lobbying. Again, the participants were asked to prioritise some specific areas and ranked on the following order partnerships between governments, industry, and academia, communication strategies, data management, public private partnerships, education of society on AMR, economic models for assessing long-term impact, regulation on antibiotic prescription pending diagnostic testing,

[7] https://engage.ifm.eng.cam.ac.uk/

advocacy on diagnostic benefits, partnerships between countries on pricing and reimbursement, and drive towards AMR testing and pathogen identification at point of care.

Building on the outcome of the Kick-Off workshop as well as the development of User Requirements and Target Product Profiles in WP 1.2., we considered the roadmap for the development of future diagnostic tests for respiratory tract infections as the pathway to achieving the desirable and aspirational Optimum Requirements in the two TPPs. Achieving these reside on three pillars: technology, business and regulations. Technology R&D must develop rapid tests that deliver lab-quality results quickly in point-of-care settings. However, funding for emerging companies is low, making it difficult to advance new technologies. Funding is also crucial to meet regulatory requirements, which are now more localised and diverse, limiting access to multiple regional markets and raising entry costs. Better reimbursement policies are needed to ensure quicker adoption of new diagnostics. All of the three pillars technology, business and regulations must interrelate in a collaborative ecosystem to achieve the desirable TPP criteria discussed in the next paragraphs.

Respondents in our user needs survey in WP1.2 showed a strong desire for an instrument-free test that covers both Upper Respiratory Tract Infections (URTI) and Lower Respiratory Tract Infections (LRTI) using a single, non-invasive sample type such as nasal swabs or saliva. While this is understandable from a user perspective to have a simple test that covers all eventualities of a patient presenting with respiratory symptoms, it poses the crucial challenge that so far, there is no single sample type which allows detection of the etiologic pathogens for URT and LRTI. Funders have recognised this need[8]. For the analytical targets, there is a trend towards multiplex detection of biomarkers, bacterial and viral pathogens, and antibiotic resistance determinants. Technologically, this is challenging as it requires multiparameter detection and requires the simultaneous or rapid sequential analysis of multiple detection points. All these features add to the technical complexity of the test which is difficult to integrate into an instrument free test especially as there is a demand to move beyond the current qualitative testing to quantitative detection. As the requirements on point of care diagnostics rise, a strong demand on quantitative results is desired. These will enable for example the determination of the severity of infection based on the host response as well as pathogen load. Simplification of the preanalytical phase will progress to achieve minimal sample preparation requirements with no more than three manual steps and no precision steps. As a whole, the strong drive to faster test results to provide answers within the patients' visit is reflected in a time to result of less than 10 min. Finally, increased requirement specifications on sustainability, and ambient, energy neutral storage conditions will have to be met.

In addition to technical requirements, manufacturers of IVD products need to navigate a complex regulatory landscape that involves multiple international and national standards. They need to demonstrate the safety and effectiveness of their products, comply with quality management systems, and be prepared for regular audits by

[8] https://carb-x.org/carb-x-news/2024-funding-round/

regulatory authorities. Understanding and complying with these regulatory aspects is crucial for the successful development, registration, and marketing of IVD products.

While all the above-described requirements are quite aspirational to be achieved in their entirety in a 5-10 years' timeline for an instrument-free test, similar advanced specifications are likely to be reached earlier with instrument-and-cartridge-based tests. These offer greater technical opportunities for the integration of multiplexed and multiparametric detection and generally superior performance in terms of sensitivity and specificity and their ability for quantitative detection. To fulfil the desirable criteria, the test should also use a single, non-invasive sample type and streamline sample preparation entirely within the cartridge. This development will follow the existing concept of sample-to-answer-cartridges but is likely to make them less resource intensive and easier to handle. The instrument-and-cartridge-based tests must offer lab-quality results in under 15 minutes, i.e. within the time a patient is likely at a doctor's appointment or able to wait. Advanced connectivity options, including Wi-Fi, Bluetooth, and GSM, are essential for automatic data export and remote updates. These aspects will ever increase with the rise of real-time updated diagnostic algorithms, real-time surveillance, digital epidemiology, cloud-based services and AI.

5. Dissemination

A manuscript based on the presented work and results has been compiled and will be submitted imminently to a journal relevant to the target audience of VALUE-Dx.

6. Conclusion

We have provided a roadmap for the development of future diagnostics tests for respiratory tract infections. The roadmap is mainly based on a thorough landscape of currently available and emerging commercial in vitro diagnostic tests, an aligned assessment of product development plans and technology readiness levels and the ambitious and aspirational criteria for future tests outlined in the Target Product Profiles developed derived of the user requirements determined in WP1.2. In conclusion, we believe that the roadmap presented here and soon published in the peer review, open access literature provides necessary guidance for future development, implementation, and increased uptake of CA-ARTI diagnostics. This will help reduce unnecessary antibiotic use and improve patient benefits overall.

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