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Implementing cardiovascular precision diagnostics: laboratory specialists as catalysts?

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Balanced clinical and analytical performance requirements of medical tests?

Laboratory specialists in medical labs are accountable for state-of-the-art test menus composed of safe and clinically effective medical tests that are fit-for-clinical-purpose and bring along a favourable benefit/harm ratio for patient management and outcome. A cyclical test evaluation framework, encompassing five interdependent key elements of test evaluation, was developed by the EFLM Working Group on Test Evaluation as a comprehensive tool for test evaluation.[1] In essence, predefined clinical performance specifications mentioned in clinical guidelines should be accompanied by matching analytical performance recommendations of the test. As clinical needs and intended uses of medical tests in clinical care pathways evolve in periodically updated IVD-containing clinical guidelines, it is important that analytical performance characteristics of medical tests keep pace with revised clinical guidelines and new demands. In the case of cardiovascular risk management (CVRM), the routine serum lipid profile – consisting of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDLc) and high-density lipoprotein cholesterol (HDLc) – is without prejudice pivotal in most clinical dyslipidaemia guidelines since the 90s of the past century, based on evidence generated by epidemiological studies, population studies and clinical trials.[2]

Clinical practice guidelines for lipid testing started with the USA National Clinical Education Program (NCEP) in 1985.[2] Subsequently, Adult Treatment Panel I, II and III clinical guidelines appeared, followed by AHA/ACC (in 2013 and 2018) and European EAS/ESC and EAS/EFLM guidelines (in 2016 and 2019, respectively) on CVD prevention.[3–5] Current clinical guidelines rely on blood LDLc values as primary target to guide treatment decisions and goals.[6] The updated 2019 ESC/EAS guidelines recommend a move towards intensive lowering of LDLc, which is warranted on scientific grounds and achievable in clinical practice. These present a further challenge since they recommend aggressive goals for LDLc lowering: <1.8 mmol/L (<70 mg/dL) for patients at high risk of atherosclerotic cardiovascular disease (ASCVD); <1.4 mmol/L (<55 mg/dL) for patients at very high risk or with clinically evident ASCVD and <1.0 mmol/L (<40 mg/dL) for very high-risk patients who experienced a second vascular event within 2 years. Surprisingly, recommendations on analytical performance are unchanged since 1990 for TC[2] and since 1995 for LDLc, HDLc and TG.[2,7–9] No revised analytical performance recommendations were made for more than 25 years, notwithstanding multiple clinical guideline updates which currently demand intensive LDLc lowering to *on-treatment* goals as low as ~1–1.5 mmol/L.[10] Note that the originally recommended NCEP analytical performance criteria for LDLc (CV_a < 4%; bias < ±4% bias and total allowable error < ± 11.8%) at which to consider drug therapy (3.37–4.92 mmol/L) and *on-treatment* goals (2.6–4.14 mmol/L) are for 2.5 to 4-fold higher decision limits compared to currently recommended decision limits.[2,7,10]

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Metrological traceability of test results starts with defining the measurand

Another inconvenient truth is related to the operational definition of LDL, based on physical density-based separation of lipoproteins using ultracentrifugation: lipoproteins in the density range 1.019–1.063 g/mL are historically defined as LDL, whereas lipoprotein (a) (Lp(a)) is defined as having a density range of 1.045–1.080 g/mL, which partially overlaps with the LDL density range. Confounding of LDL also occurs in case of concomitant presence of intermediate density lipoproteins (IDL; d = 1.006–1.019 g/mL)) and dysbetalipoproteinemia with elevation of remnant lipoproteins.[2]

The Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, USA, developed a beta-quant reference measurement procedure in the 2nd half of the past century, which is still worldwide in use in the global CDC Cholesterol Reference Method Laboratory Network (CRMLN) for standardization of commercial LDLc tests. Notwithstanding the adequate Lipid Standardization Program led by CDC, both calculated and direct LDLc tests suffer *by design* from non-selectivity and faulty assumptions. From CAP and CDC surveys using commutable, value-assigned specimens, it became obvious that LDLc results are inaccurate and exceed allowable measurement uncertainty at low levels, especially in case of hypertriglyceridemia.[11] As accurate and reliable blood LDLc tests are critical for the correct assessment of cardiovascular risk and the appropriate treatment of patients, better and more robust biomarkers are needed. Especially, the analyte intended to be measured should be unequivocal, unaffected and molecularly defined. The clinical implication of reporting *so-called* LDLc, confounded by cholesterol contributions from other lipoproteins, is causing imprecision medicine with misclassifications and flawed conclusions on the therapeutic efficacy of lipid lowering drugs. In the case of elevated LDLc due to high Lp(a)-cholesterol, statin therapy resistance may erroneously be suspected.

Evolution in science and metrology

Transitioning to precision diagnostics is needed to make biomarker-based cardiovascular risk management more effective. Therefore, a well-defined, molecular definition of biomarkers in dyslipidaemia tests and scientific validity (i.e. association of the promising biomarker with the disease) are fundamental requirements for cardiovascular precision diagnostics. To that end, measuring functional serum apolipoproteins rather than lipoprotein cholesterol fractions should conceptually be a logical step towards refining dyslipidaemia diagnoses and treatments.[12] In that context, apolipoprotein B (apoB) is recognized as a well-defined functional biomarker of LDL particle clearance and a measure of atherogenic particle number. From a metrological viewpoint, apoB is by far superior to LDLc and for any patient with triglycerides >1.5 mmol/L, either apoB or non-HDLc (= poor man's apoB) are the preferred parameters for screening.[13] Yet, so far no IVD-manufacturer has invested in setting up a randomized control trial (RCT) to demonstrate apoB's superior clinical and cost effectiveness above that of LDLc. Is relying on an old operational definition and pretending accuracy at low LDLc levels which confuses and misleads clinicians good laboratory practice? If the measuring tool is not robust enough, why stick to old dogma's?

Lp(a) is another new kid on the block for biomarker-based CVRM in both the 2022 European EAS consensus and Canadian dyslipidaemia guidelines, respectively.[14–15] Lp(a) underwent a renaissance as new light was shed on its pro-atherogenic and prothrombotic role with reinvestigation of its clinical relevance in clinical trials using molar Lp(a) tests that are marginally affected by apo(a) size polymorphism.[16] Lp(a) measurement is now recommended once in a lifetime, as part of an initial lipid screening to assess cardiovascular risk. The intention is to identify high-risk patients in order to treat them with specific Lp(a) lowering therapy in the nearby future (in 2025, new Lp(a) lowering drugs will be available).[16] Lp(a) measurement can hence be seen as an exemplar and first step into cardiovascular precision medicine. It is anticipated that other apolipoproteins will follow: in case of apo CIII excess and increased VLDL remnants, anti-sense oligonucleotide therapies are looming on the horizon for more personalized and effective treatment of these hypertriglyceridemic patients.[16]

Evolution in healthcare

The vision that medicine should be predictive, preventive, personalized and participatory ('P4') has long been advocated by Leroy Hood and other pioneers of systems medicine.[17–19] Until recently, these pioneers were described as voices in the wilderness. Yet, that is no longer the case. The major elements of this vision of P4 medicine have been largely adopted by a series of reports by the US Institute of Medicine (IOM) and the National Academy of Sciences. In addition, P5 medicine is currently promoted as an eHealth concept able to engage patients even more in their personalized treatment as well as management plans: patients should become competent, active, responsible managers of their own health. Analysing and improving quality of life should no longer be a secondary but a primary objective of the care process.[20]

Evolution in regulatory requirements

IVD-manufacturers and end-users in medical labs are facing stringent legislation that regulates market access of IVDs. IVD Regulations differ across the globe, the most stringent ones being the US and Chinese FDA and the European IVDR. In Europe, a phased role out of the IVD Regulation 2017/746 is ongoing since 2022. Major changes are the requirement of independent third party assessment of nearly all commercial tests by notified bodies and/or competent authorities on IVDR compliance. On top, during the entire life cycle of tests, IVD-manufacturers are expected to perform post-market follow-up surveillance. Hopefully, the IVDR will have a positive impact on allowing only reagents with updated and aligned analytical performance specifications of commercial tests with clinical performance requirements mentioned in updated clinical guidelines.

Lab specialists as game changers for cardiovascular precision diagnostics?

For implementing cardiovascular precision diagnostics, critical reports of imperfect medical tests for specific intended uses should be published and communicated with IVD-manufacturers, clinicians, lab specialists and regulators. In the case of CVRM, neither direct or calculated LDLc or Lp(a)-corrected LDLc are *fit-for-clinical-purpose* at ~1 mmol/L *on-treatment* goals, especially in target populations with metabolic syndrome, diabetes mellitus or hypertriglyceridemia. Lab specialists should dare to break the silence and contribute to appropriate diagnostic care, aligned with the state of science and the state of metrology. Restricting conventional LDLc tests to original clinical indications where the test meets the clinical performance requirements and meanwhile introducing selective, accurate and robust Lp(a) and apoB tests for new intended uses will facilitate clinicians to make a more comprehensive CVD risk assessment and install more personalized and effective treatments in patients at risk.

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