VALUE of DIAGNOSTICS (including Rapid Diagnostic Tests, *RDT*):
defining, demonstrating, & linking to registration and reimbursement

Jean-Louis Tissier
VP, Public & Government Affairs

GLOBAL BURDEN OF BACTERIAL INFECTION

SECOND LEADING CAUSE OF DEATH GLOBALLY

Bacterial infection is the second cause of death after ischemic heart diseases and before strokes.

33 MAIN BACTERIAL PATHOGENS

ARE ASSOCIATED WITH

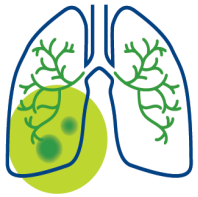
7.7 MILLION DEATHS PER YEAR

(estimate) across the 11 infectious syndromes studied

MAIN SYNDROMES

3 SYNDROMES

were responsible for 75% of bacterial related death in 2019:



1. LOWER RESPIRATORY INFECTIONS*
> 2 millions

2. BLOODSTREAM INFECTIONS
> 2 millions

3. PERITONEAL AND INTRA-ABDOMINAL INFECTIONS
> 1 million

* not including tuberculosis

DIAGNOSTIC TOOLS ARE ESSENTIAL

To prevent and manage bacterial infections, it is important to identify the causative pathogen.

IDENTIFY

the type of bacteria causing the infection

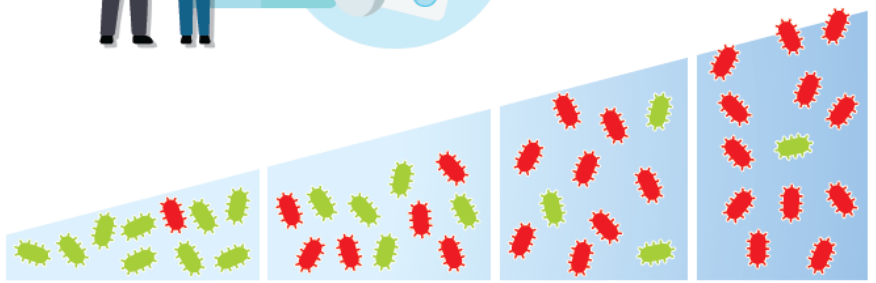
Staphylococcus aureus | *Escherichia coli* | *Streptococcus pneumoniae* | *Klebsiella pneumoniae* | *Pseudomonas aeruginosa*

GUIDE

the clinical team in selecting the most appropriate treatment

PREVENT

selective pressure on bacterial species increasing antibiotic resistance



FIGHTING ANTIMICROBIAL RESISTANCE

CAUSES OF ANTIBIOTIC RESISTANCE

TACKLING ANTIMICROBIAL RESISTANCE – IVD HAS A KEY ROLE TO PLAY

*"I am frequently asked by people "what is the **single most important of the ten points** to tackle resistance?"*

*If I had to pick one that was more important than the others… I'd say **"diagnostics"…***

Lord Jim O'Neill

(*TACKLING DRUG-RESISTANTINFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS*, 2016)

- Public Awareness
- Sanitation and hygiene
- Antibiotic in agriculture and the environment
- Vaccines and alternatives
- **SURVEILLANCE**
- **RAPID DIAGNOSTICS**
- Human capital
- Drugs
- Global innovation fund
- International coalition for action

BARRIERS TO RDT USE IN HICS AND LMICS

The EWG agreed that global RDT use could be increased and outlined several barriers to RDT use across HICs and LMICs:

- Although some biomarkers like procalcitonin and C-reactive protein are included in the World Health Organization (WHO) Model List of essential *in vitro* diagnostics (EDLs), **they are not mandated for use** [8].
- The **LMIC representatives** of the EWG **support the inclusion of non-molecular RDTs and other biomarkers** in the WHO Model List of EDLs [8].

Moore LSP, Villegas MV, Wenzler E, et al. Rapid Diagnostic Test Value and Implementation in Antimicrobial Stewardship Across Low-to-Middle and High-Income Countries: A Mixed-Methods Review. Infect Dis Ther. Published online June 1, 2023. doi:10.1007/s40121-023-00815-z

VALUE OF DIAGNOSTICS TO SUPPORT ANTIMICROBIAL STEWARDSHIP

Diagnostic testing has a key role to play!

ANTIMICROBIAL STEWARDSHIP (AMS) IN PRACTICE…*FOR THE RIGHT PATIENT*

A set of interventions for improving antimicrobial prescribing:

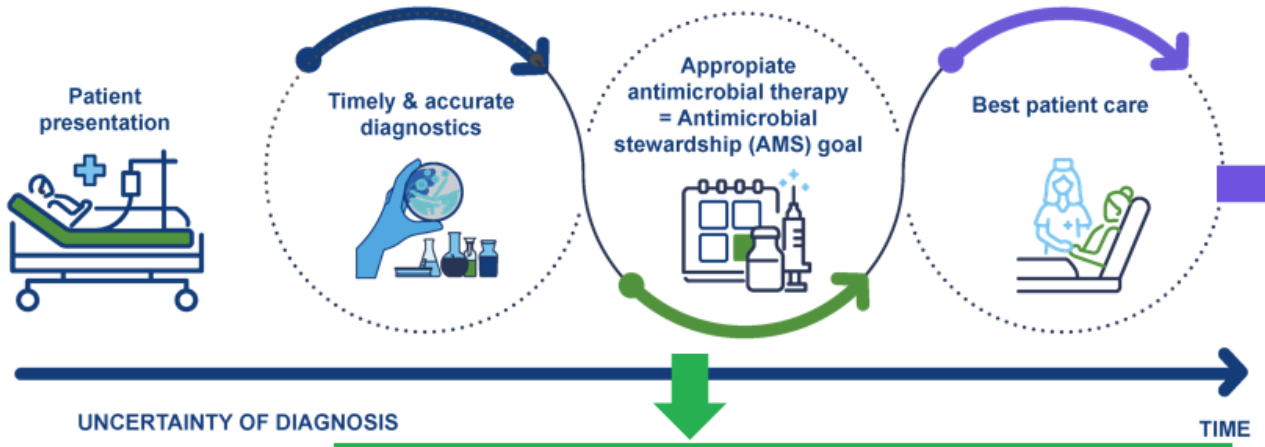
- → **Right antimicrobial (antibiotic)**
- → **Right indication**
- → **Right dose & route**
- → **Right duration**
- → **Causing the least harm to the patient and future patients**

APPROPRIATE THERAPY

Diagnostics contribute to better outcomes

Diagnostics contribute to higher medical value leading to better patient care [13]

[14]



PATIENT OUTCOMES [15,16]

- Clinical resolution/cure rate
- Hospital length of stay (LOS)
- Morbidity
- 30-day (d) mortality
- Time to discharge
- Re-admission at 30 d
- Patient safety
- AE [healthcare-associated infections (HAIs), *Clostridioides difficile (C difficile)*, acute kidney injury]
- Quality of life post-care

ANTIMICROBIAL PRESCRIBING INDICATORS [15,16]

- Antibiotic therapy initiation rate
- Time to appropriate therapy
- Proportion of appropriate antibiotic therapy
- Antibiotic exposure
- Length of therapy
- De-escalation/escalation
- Time to oral switch
- Reduction in antimicrobial use: days of therapy (DOT), defined daily dose (DDD)

Adapted from bioMérieux S.A.. Available at https://www.biomerieux.com/content/dam/biomerieux-com/medical-affairs/amr/educational-materials/evidence-based-diagnostics-for-ams-offered-by-biomerieux.pdf. bioMérieux SA property

AE, adverse event; **AMS**, antimicrobial stewardship; ***C difficile***, *Clostridioides difficile*; **d**, day; **DDD**, defined daily dose; **DOT**, days of therapy; **HAI**, healthcare-associated infection; **LOS**, length of stay.

References **13-16** are available in the References Section.

This content is intended for Healthcare Professionals only

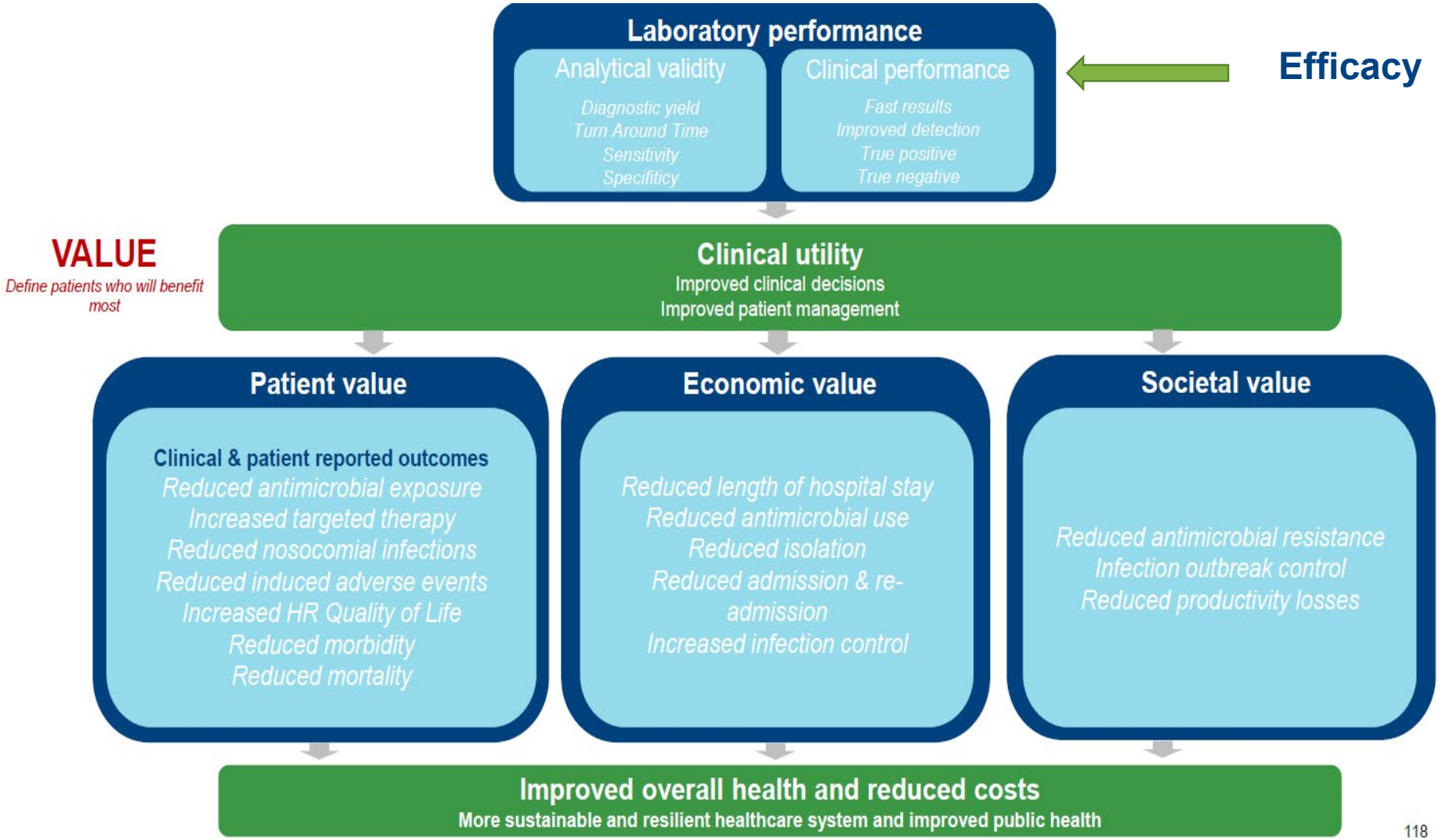
ADOPTION OF NEW MEDICAL APPROACHES NOW BASED ON MEDICO-ECONOMIC VALUE

THE OBJECTIVES OF ANY HEALTHCARE INTERVENTION

Health Benefits

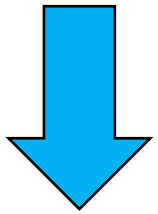
Economic Benefits

HEOR VALUE FRAMEWORK



HEALTHCARE "VALUE" : MEDICO-ECONOMIC VALUE

- Well-established for most **drugs**
- Well-established for most **vaccines**
- Well-established for most **medical devices**
- Less well-established for **in vitro diagnostics (IVD)**



- ***Medico-economic value of IVD not well established or recognized***
- **Regulatory registration** of IVD is usually not linked to this « value »
- **Reimbursement** of IVD is not linked to this « value »

OBVIOUS VALUE DISCREPANCIES BETWEEN THERAPEUTICS AND IVDs (USA example)

THERAPEUTIC EXAMPLE

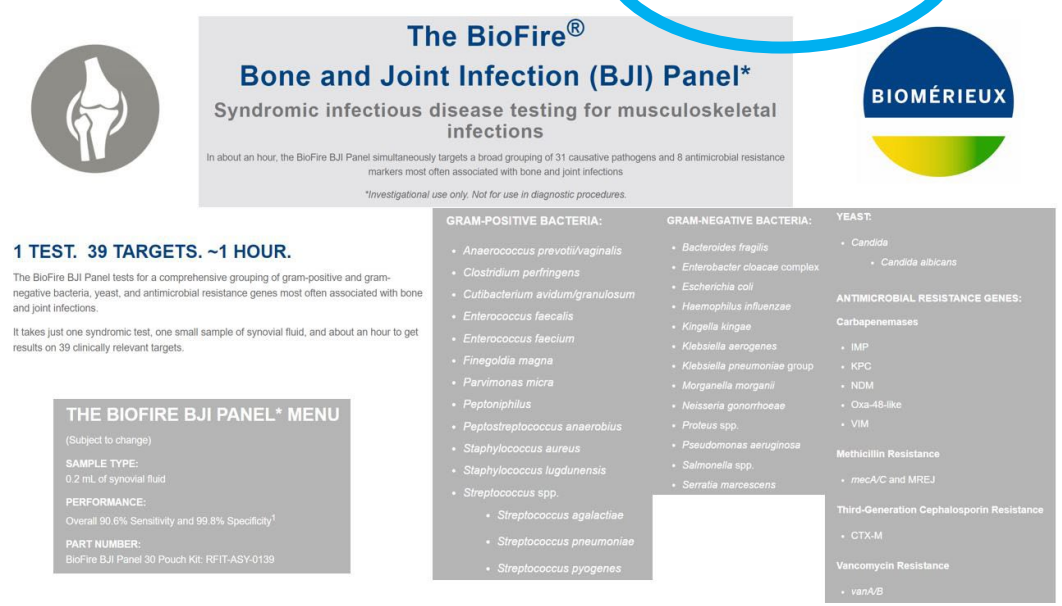
- New genetic treatment of hemophilia B

World's Most Expensive Drug Approved to Treat Hemophilia at $3.5 Million a Dose

- CSL Behring's hemophilia B treatment Hemgenix approved by FDA
- Hemgenix is one-time gene therapy administered by IV infusion

IVD EXAMPLE

- New IVD to detect 31 possible infectious pathogens of septic joints with 8 resistance genes
- Reimbursement approx. $285



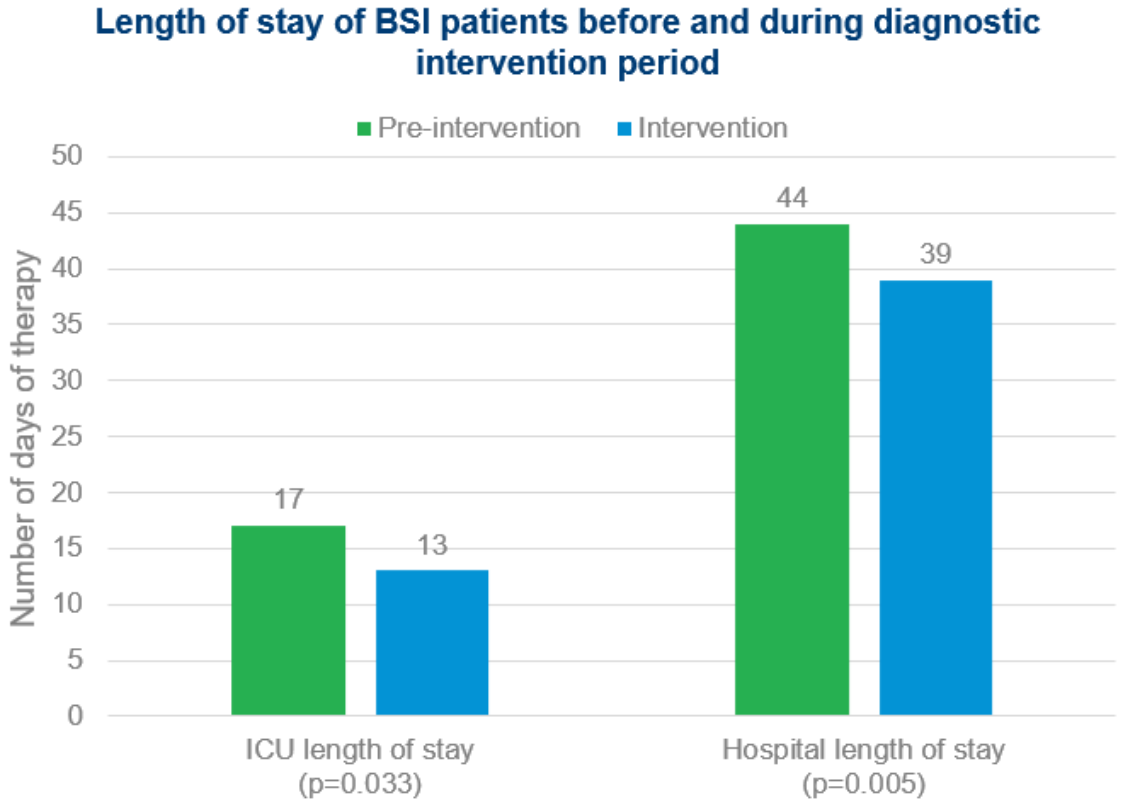
RAPID DIAGNOSTIC TESTS CAN REDUCE LENGTH OF STAY AND ANTIMICROBIAL CONSUMPTION IN PATIENTS WITH BSI

Background

- Pre–post quasi-experimental study of rapid diagnostic tests (MALDI-TOF and detection of resistance genes) (n=102 episodes of bacteremia in the intervention period) compared with the pre-intervention period (n=114 episodes)
- **Main outcomes:** Hospital and ICU length of stay after blood culture positivity, and antimicrobial consumption

Key findings

- **Antimicrobial consumption was significantly lower in the intervention period** (1262 vs 1381 DOT/1000 days; p=0.032)
  - Consumption of **carbapenems** (543 vs 846 DOT/1000 days; p=0.040)
  - Antimicrobials against **Gram-positive organisms** (270 vs 475 DOT/1000 days; p=0.004)



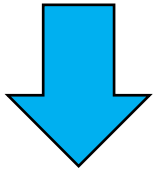
AMS, antimicrobial stewardship; **DOT**, days of therapy; **ICU**, intensive care unit; **MALDI-TOF MS**, matrix assisted laser desorption ionization-time of flight mass spectrometry.
Reference **19** is available in the References Section

Campos AF, Arantes T, Cambiais AMVB, Cury AP, Tiroli CG, Rossi F, et al. Impact of an Antimicrobial Stewardship Program Intervention Associated with the Rapid Identification of Microorganisms by MALDI-TOF and Detection of Resistance Genes in ICU Patients with Gram-Negative Bacteremia. Antibiotics (Basel). 2022;11(9):1226.

VALUE-BASED APPRECIATION OF AN IVD DEPENDS ON…..

Health Economic Evaluation

- ……**routine HTA** (Health Technology Assessments) of novel or costly IVDs
- ……acceptable **defined HTA methods** for determining VALUE of an IVD
- ……**standardized HTA methods** for VALUE determinations between countries



Medico-Economic Value

- ……link between **VALUE** and **regulatory registration**
- ……link between **VALUE** and **reimbursement** by various payors

MULTIPLE FACTORS IMPEDING DETERMINATION OF VALUE FOR IVD PRODUCTS

- IVDs are used **among many other interventions** (lab tests, imaging, devices, therapeutics) which determine ultimate health & economic outcomes
- Historically and "traditionally", IVDs are **reimbursed according to the technology** or platform used, rather than their medico-economic value
  - e.g. all immunoassays are thrown into the same basket; an immunoassay for Vitamin D is valued and reimbursed the same as an immunoassay for Procalcitonin in order to reduce antibiotic use and AMR
- Historically and "traditionally", IVDs are **evaluated only technically** (sens, spec, PPV, NPV, precision, accuracy) and not on the health-economic value which they bring
- Difficulty in establishing **criteria and definitions of "value" for IVDs** because:
  - they are extremely heterogeneous in use (screening, diagnosis, prognosis, follow-up)
  - they are extremely heterogeneous in their impact on individuals, families, communities, globally (patient outcomes, lack of spread to contacts, impact on outbreaks & AMR & etc.

OUR "ASK"

- **Robust, harmonized, standardized HTAs of IVDs** to consider all of the dimensions of "value"
- **IVD-specific HTAs** taking into account particularities & heterogeneity of IVDs and their uses
- **Geographic and economic considerations** should be taken into account for HTAs
- Some key **Market Access** issues (regulatory registration, reimbursement, government support, payor coverage, etc) should be **tied to the HTA outcomes** in some way
- Traditionally expensive, long, complicated clinical studies for HTAs and evaluating novel diagnostics must be replaced by shorter, more efficient, **creative HTA methods** of determining medico-economic value, such as:
  - Smaller randomized clinical trials
  - Prospective observational studies
  - Retrospective data evaluation during the pre-registration period
  - Meta-analyses to combine various studies, increase power and improve value determination
  - Encouragement of Consensus Statements, White Papers, Clinical Guidelines by experts and KOLs to facilitate clinical adoption
  - Patient-reported evidence (PROMs, PREMs)

HTA CREATION, COORDINATION AND OVERSIGHT

- Although HTAs should be performed and analyzed by independent recognized and respected national or regional bodies, they must receive input and be endorsed by multiple stakeholders:
  - Patients and patient groups
  - Health provider organizations (hospitals, clinics,)
  - Clinical laboratories
  - Healthcare professionals and their societies/associations
  - Payors (governmental and non-governmental), and agencies involved in reimbursement and policy
  - Other HTA agencies
  - Regulators
  - Quality Standards Organizations
  - **IVD manufacturers**

THE ROLE OF IVD DEVELOPERS SHOULD INCLUDE:

- The right to request an HTA
- The right to contribute to the study methodology
- The right to review & comment on all stages of the results during a public consultation phase, before final conclusions are drawn
- The right to provide expertise and data to the evaluating HTA body for consideration during the assessment process (especially when industry data is not in the public domain)

Thank you.

PIONEERING DIAGNOSTICS