Discovery and Clinical Utility Testing of Biomarkers for NTD Elimination

Session Date: Saturday, October 27

Session Time: 1:00pm – 4:00pm

Session Location: Rosalie, 3rd Floor

Session Description: This session aims to highlight the current state of development for diagnostics and biomarkers for neglected tropical diseases (NTDs). Trends in biomarker discovery and development will be reviewed. In addition, inefficiencies in the current approach for developing NTD diagnostic tools will be discussed and alternatives for an optimized development framework explored. The gap between biomarker discovery and active diagnostic development will be discussed with a focus on how can the NTD community better enable a streamlined approach to biomarker discovery and development.

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KEY DISCUSSION POINTS

<u>Use cases of a biomarker of adult female worms for the elimination of onchocerciasis (Paul Cantey)</u>

- Onchocerciasis programs at different stages need diagnostics with different qualities for different use cases
    - Mapping needs to be sensitive due to low expected prevalence and specific to not cross-react with co-endemic parasites such as *Loa loa.*
    - Monitoring and impact assessment using skin snip in 5 to 9 year-olds is specific but it would be better to have a marker that develops sooner for timely impact assessment; it would also be beneficial to have marker that would identify adult worms.
    - Diagnostics for stopping treatment need to be both sensitive and specific, and it would be beneficial to have a marker that could identify female adult worms that are reproductively active.
    - Post-treatment surveillance could be done in blackflies, but the concern would be local capacity to perform assays (entomology capacity and lab capacity). A human biomarker against female adult worms would also be beneficial.
    - Post-elimination surveillance in blackflies is currently suggested by the World Health Organization (WHO). A good development would be to be able to utilize a blood test (using dried blood spots) that could be integrated into other surveillance platforms to reduce costs.
    - For mop-up and monitoring cure, a test is needed that could function as a diagnostic for individuals. For treatment a macrofilaricide would be helpful.

Elimination biomarkers for STH: Discovery of non-stool based biomarkers to be used in low-intensity, low-prevalence soil-transmitted helminthiasis (STH) infection settings (Lieven J. Stuyver)

- STH control needs new diagnostics that cover different use cases.
- A diagnostic more sensitive than Kato Katz but not cost prohibitive (e.g., PCR) is needed.
    - Detect antigen in urine
    - Detect antibodies or antigen in blood
- Development of new diagnostics follows a defined process which requires multiple panels of well-characterized positive reference samples (e.g., different panels are needed at discovery versus validation steps for unbiased results).
- Proper planning and access to panels are needed at the beginning to avoid bottlenecks in workflow.
- Target product profiles should be discussed with different subject matter experts.
- Access to needed reference samples can take years to negotiate; open access biobanks would address this difficulty.
- Lessons learned in one area should be applied to next project (e.g., an algorithm using multiple peptides needed for sensitive and specific onchocerciasis antibody diagnosis would inform planning for same work for STH peptide screening).

Biobanks requirements to demonstrate intended use claims for elimination biomarkers for O. volvulus and STH (Judd Walson)

- People who donate reference specimens usually do so for the benefit of medical research in general.
- Many isolated private repositories exist, but access to physical samples and information about them is limited. Sharing between different institutions is challenging due to international laws regulating human tissue as property.
- A biobank would help address these difficulties and allow researchers to more easily access the samples they need to move research forward.
- HIV is a good example of well-functioning system.
- Well-regulated and networked and samples from clinical trials can be requested by those conducting research.
- Well-funded biobanks exist:
    - NTDs lack the networked trials and extensive shared biobanks of HIV.
    - Considerations for creating biobanks or more accessible sample sets
- Biobanks could be distributed in different physical locations but still searchable in a single central database.
- Different countries' laws would need to be taken into account, as well as differences in sharing materials with academic versus commercial institutions.
    - Identify which countries may have the most restrictive prohibitions on sample transfer at outset.
- This effort will need strong human capital investment to perform governance of complex systems.
- Standard language for materials transfer agreements, sample disposition, and data sharing based on broad consent (e.g., "Sample will be stored and destroyed within five years of disease of interest being eliminated") would be necessary.
- It may be unrealistic to expect costs to be recovered.

KNOWLEDGE GAPS IDENTIFIED

- A biomarker that can recognize adult female worms (need not be exclusively females as long as adult worms can be detected) OR some other proxy that can estimate adult worm burden
- Macrofilaricide or drug to kill/sterilize adult female worms
- A test for individual diagnosis and treatment monitoring
- Target product profiles need to have extensive input from subject matter experts
    - Biomarkers for STH could be array of peptides with algorithm or analysis ***OR*** a more pan-helminth marker that could cover most species of interest
- Open access to shared biobanks would be beneficial to effective diagnostic development
- A searchable database of biobanks would be key (use pre-existing models)
- Need to consider incentives for different types of participants (e.g., academic vs commercial; groups with biobanks that would need to invest time and funds to prepare large sample sets)
- Need to consider protections for low- and middle-income countries wary of being taken advantage of
- Need to discuss and come to consensus on who would provide governance

RECOMMENDED NEXT STEPS

O. volvulus

1) Support the validation of existing and newly identified biomarkers of Ov adult female for monitoring & evaluation.
    a. Demonstrate specificity
    b. Assess changes post-treatment (particularly macrofilaricidal therapies like doxycycline)
2) Support the validation of new (or newly identified) biomarkers that could be used to in making treatment stopping decisions
3) Support the validation of existing (or newly identified) biomarkers that could be used in post-treatment and/or post-elimination decision making
4) Create a virtual biobank across multiple laboratories tied to information/metadata about samples

STH

1) For all use cases, quality control/assurance programs need to be put in place for both stool-based microscopy approaches (i.e., Kato-Katz) and for qPCR
2) Biobanks (virtual or real) for post-treatment surveillance
3) Support the validation of new (or potential) biomarkers for use in post-treatment surveillance
4) Support the development of sets of SOPs for collection, storage, consent language

STH Breakout Notes

- Use case 1 – mapping
  - Kato Katz is okay for case 1 but could be improved.
  - Pooling could help feasibility (i.e. reduce cost) but need to be careful to maintain quality of data, needs to be done at central laboratory,
- Use case 2 – monitoring program
  - Kato Katz insufficient for monitoring impact of deworming programs
  - How sensitive does potential diagnostic have to be?
  - Stool could be used to understand both infection as well as transmission potential and understanding transmission dynamics would be important at this stage
  - Overall, qPCR on stool may be the best option for use case 2 because it already exists and gives us the information we need. Just need to be firm about justifying cost. There is some local capacity to perform this.
- Use case 3 – stopping decisions
  - Kato Katz is insufficient for monitoring if transmission is broken
  - qPCR on stool would still be adequate despite cost, but stool is a challenging sample type to collect and people may be less willing to participate as transmission gets low
- Use case 4 – post-treatment surveillance
  - This is the area for new tools, where biggest gap exists
  - Need for biobanks are needed for this stage but many challenges exist depending on source of samples and institution request samples
    - Need SOP for collection, storage and consent language
    - Need to have a third party group to govern/administer and facilitate broad participation in biobank
    - Name "biobank" may have bad connotation; alternative?
  - What secretory targets could be investigated as potential biomarkers? ELISA measuring secreted antigen in stool would be useful to develop.
  - How do indirect semi-quantitative markers (e.g. ELISA OD) relate to intensity of infection?
  - Could urine be a useful sample type to look for biomarkers?
  - Serology works well in other worms (e.g. strongyloides) but STH has gaps
    - Current limitations are that known targets are cross-reactive, antibody responses are long lived
    - Peptides arrays analysed with algorithms used for
  - Genomes would be useful to identify biomarkers; need to
- Misc
  - Are there opportunities for integration when stool is the sample type collected?
  - Mapping and monitoring programs could be done locally but stopping and post-treatment surveillance would be better done by centralized lab with consistent standard operating procedure.

O. volvulus Breakout Notes

Discussion centered around priorities for new and/or existing tests based on various use cases. It was noted that for any given use case that there should be clear understanding about sets of samples that would be needed to validate a given new (or existing) biomarker.

1. Priorities for Ov tests/biomarker based on use case scenarios (M&E/Stop treatment/Post-treatment Surveillance/Post-Elimination Surveillance). Major focus to be on Ov-adult or fertile Ov-female targeted molecules
   a. Use Case 1 -M&E

1. Specificity is crucial – required a highly specific test that identifies adult females
2. Sensitivity per se is not the critical variable but whether it changes over time

b. Use Case 2 - Stopping Treatment
   1. High degree of sensitivity and specificity are needed.
   2. Requires a test that can detect a biomarker that disappears rapidly
   3. Could be either an Ov-specific antigen or antibody target

c. Use Case 3 - Surveillance (Post-treatment and Post-Elimination)
   1. Target need not be adult female alone but could include mf and L3/L4 stage
   2. Could supplement entomologic data

2. R**epository for resources for testing and validation**
   a. Should it be a centralized facility? Overarching consensus à NO
   b. Decentralized/distributed across labs with a log/excel sheet(s) with information/metadata about the samples à YES
   c. A virtual biobank with buy in from sample collectors/repositors