

# Biomarkers for the Diagnosis of Tuberculosis

**Jennifer Gardiner**

Program Officer, Discovery & Translational Sciences

BILL & MELINDA  
GATES *foundation*

# Our strategic goal is to reduce global TB incidence

	Focus of efforts	Measure	Comments
	<ul style="list-style-type: none"> <li>• STOP TB Partnership's global vision of elimination by 2050</li> <li>• Baseline assumption: likely requires a shift in intervention focus i.e. elimination of latent reservoir</li> </ul>	<1 new case/million globally	Aspirational
	<ul style="list-style-type: none"> <li>• Prevention by reducing transmission and progression</li> <li>• Reducing diagnostic and treatment delays</li> <li>• Pulmonary TB</li> <li>• Public and private sectors</li> <li>• Country unit of analysis based on TBD incidence measure</li> </ul>	Decrease in # of new cases per capita <i>Accelerated rate of incidence decline</i>	<b>Prevention focused and achievable</b>
	<ul style="list-style-type: none"> <li>• Emphasis on general TB control (DOTS)</li> <li>• Diagnosis and treatment to ensure survival without regard to transmissibility</li> <li>• Pulmonary and extra-pulmonary TB</li> <li>• Country focus where highest burden of TB mortality</li> </ul>	Decrease in deaths due to TB	Insufficiently ambitious

# TB Strategy 2011-2016: Goal and vision of success

<b>Impact goal</b>	<b>Accelerate the reduction of global TB incidence</b>
<b>Vaccines</b>	1 TB vaccine candidate in phase 3
<b>Drugs</b>	1 TB drug regimen in phase 3
<b>Diagnostics</b>	<ul style="list-style-type: none"><li>• 1 new TB biomarker identified</li><li>• 2 new molecular diagnostics endorsed by WHO STAG</li></ul>
<b>Country-level Innovation in TB Control</b>	<ul style="list-style-type: none"><li>• Increase country TB budgets, particularly in India</li><li>• Catalyze uptake of innovative TB control</li><li>• New products with frugal engineering developed</li></ul>
<b>Global Access and Market Dynamics</b>	<ul style="list-style-type: none"><li>• Increase quality, stabilize costs of FDC and reduce costs of second-line drugs</li><li>• Accelerated uptake of innovation in target countries and globally</li></ul>
<b>Advocacy</b>	Funding secured for late-stage clinical trials

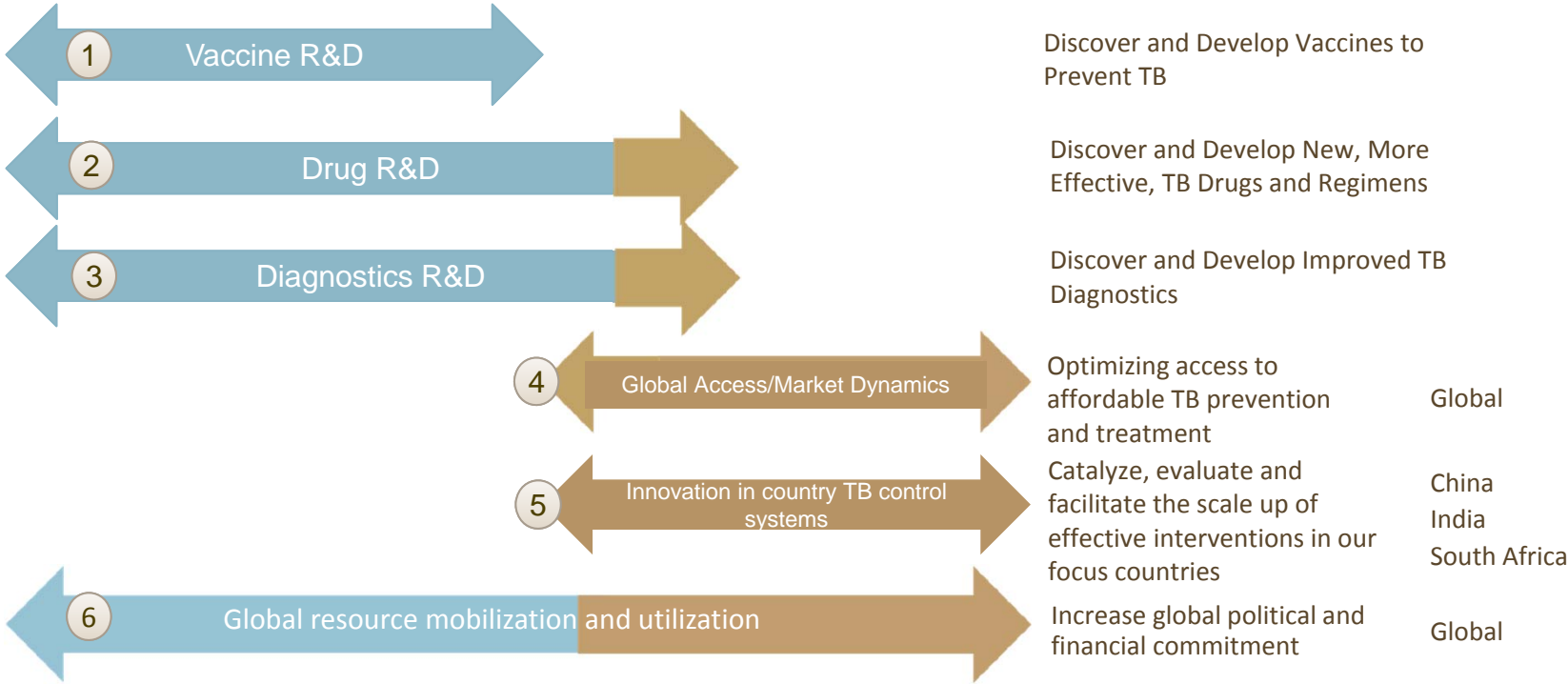
# Our TB strategic goal is to reduce TB incidence

R&D focus

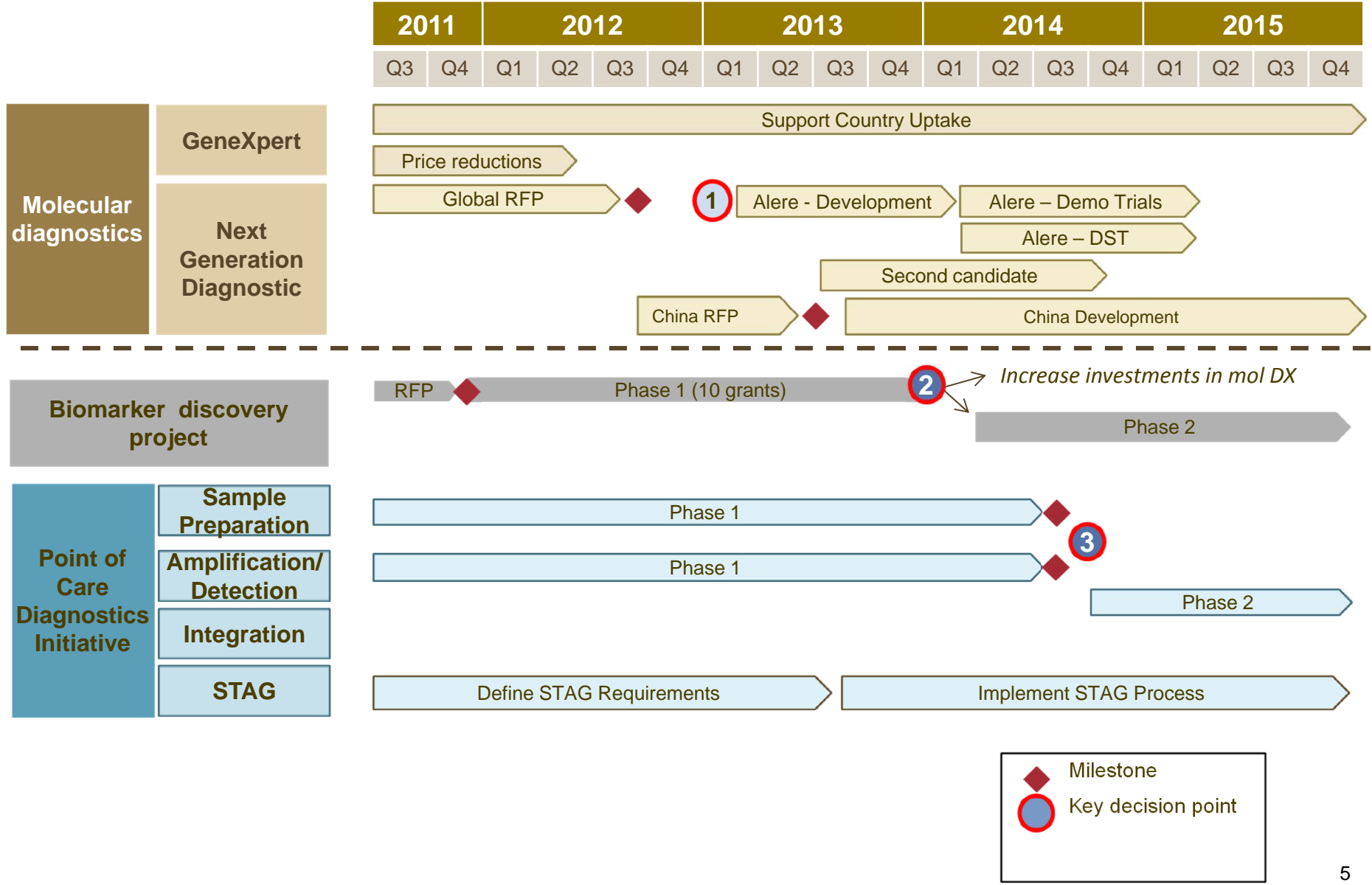
Delivery focus



Initiatives



# Diagnostic Timeline



# TB Diagnosis: *Existing solutions*

Test	Sample	Advantages	Disadvantages
Liquid Culture	Sputum, other	High sensitivity	Requires weeks to months
Smear Microscopy (most commonly used Dx)	Sputum	Low cost 2 day turn around	Low sensitivity & throughput Requires expertise and laboratory
Nucleic acid amplification (e.g. Gene Xpert)	Sputum	High sensitivity Same day results	Cost of instrument & cartridge

## Needs for biomarker research:

- High sensitivity & specificity in a low cost test that relies on either low cost or no instrument
- Test that does not rely on sputum

# Program Goal and Scope

- **Identify and validate biomarker(s) to enable development of a rapid (result within minutes to hours from sample collection), accurate, low cost diagnostic for active TB cases including HIV+ and, ideally, pediatric patients**
- **For this program, biomarker investigation is focused on blood, urine, and breath samples to enable a diagnostic that does not rely on sputum**
- **A triage test to refer a patient for confirmatory testing is also potentially within scope for the program pending further TPP refinement and impact modeling**
- **Drug resistance not explicitly included within scope for this program**

# New Grand Challenge in Global Health announced Feb 10, 2011

## ■ Biomarkers for the diagnosis of TB

- \$12M initiative, 2 phase program
- 371 applications, 21 full proposals invited
- Phase 1: 10 individual grants for up to \$750k each, up to 24 mos.
- Phase 2: expect 3-6 projects, ~\$3-4M, follow on funding for further validation of promising biomarkers



[grandchallenges.org/biomarkers](http://grandchallenges.org/biomarkers)

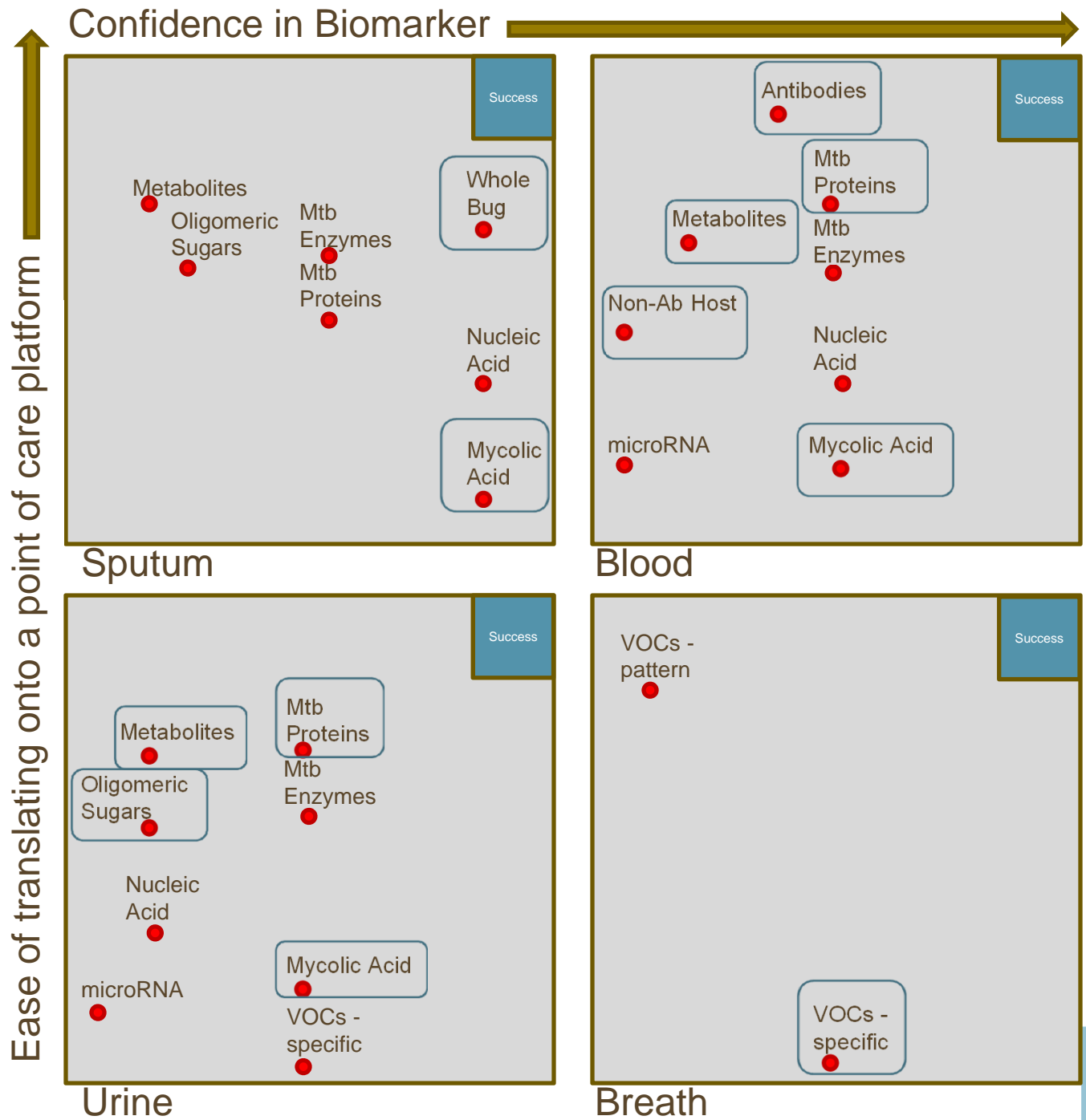




# Standardized Samples: *TB Cases & Controls*

- **Case & control definitions and procurement of samples will be key to the success of biomarker discovery/validation projects**
- **Working with FIND to provide access to well characterized banked samples and new collections, as needed, for all projects funded under this program**
- **Enable analysis of data across projects to identify potential promising combinations for Phase 2 testing**

# Biomarkers for the Diagnosis of TB Investments



# 10 Projects

500 SRM Assays  
for Mtb proteins

Plasma, Urine, Sputum  
Inst Sys Bio, Moritz

Exosomes, Mtb  
proteins by SRM

Serum, Urine  
CSU, Dobos

LAM & Mtb prot  
by aptamers

Serum, Urine  
CU, Feldheim

16 Mtb and 1200  
host proteins,  
aptamers

Serum  
Somalogic, Ochsner

Mtb cell surface  
by Ab magnetic  
beads

Sputum  
Rutgers, Alland

Novel Ab class to  
Mtb prot, by elisa

Serum  
Burnet, Anderson

Volatiles in breath  
by Mass Spec

Breath  
Louisville, Graham

Mycolic acids &  
metabolites, MS

Serum, Urine, Sputum  
CSU, Belisle

Mtb proteins by  
Ab, Simoa assay

Urine  
Forsyth, Campos

Ab to Mtb lipids,  
synthetic arrays

Serum  
Alberta, Lowary

## Pathogen

500 SRM Assays  
for Mtb proteins

Plasma, Urine, Sputum  
Inst Sys Bio, Moritz

Mtb cell surface  
by Ab magnetic  
beads

Sputum  
Rutgers, Alland

Exosomes, Mtb  
proteins by SRM

Serum, Urine  
CSU, Dobos

LAM & Mtb prot  
by aptamers

Serum, Urine  
CU, Feldheim

Mtb proteins by  
Ab, Simoa assay

Urine  
Forsyth, Campos

Volatiles in breath  
by Mass Spec

Breath  
Louisville, Graham

## Pathogen + Host

16 Mtb and 1200  
host proteins,  
aptamers

Serum  
Somalogic, Ochsner

Mycolic acids &  
metabolites, MS

Serum, Urine, Sputum  
CSU, Belisle

## Host

Novel Ab class to  
Mtb prot, by elisa

Serum  
Burnet, Anderson

Ab to Mtb lipids,  
synthetic arrays

Serum  
Alberta, Lowary

## Blood

Novel Ab class to Mtb prot, by elisa

Serum  
Burnet, Anderson

16 Mtb and 1200 host proteins, aptamers

Serum  
Somalogic, Ochsner

## Urine

Mtb proteins by Ab, Simoa assay

Urine  
Forsyth, Campos

Ab to Mtb lipids, synthetic arrays

Serum  
Alberta, Lowary

## Blood + Urine

LAM & Mtb prot by aptamers

Serum, Urine  
CU, Feldheim

Exosomes, Mtb proteins by SRM

Serum, Urine  
CSU, Dobos

Mycolic acids & metabolites, MS

Serum, Urine, Sputum  
CSU, Belisle

## Sputum

Mtb cell surface by Ab magnetic beads

Sputum  
Rutgers, Alland

500 SRM Assays for Mtb proteins

Plasma, Urine, Sputum  
Inst Sys Bio, Moritz

## Breath

Volatiles in breath by Mass Spec

Breath  
Louisville, Graham

## Protein

Mtb proteins by  
Ab, Simoa assay

Urine  
Forsyth, Campos

16 Mtb and 1200  
host proteins,  
aptamers

Serum  
Somalogic, Ochsner

500 SRM Assays  
for Mtb proteins

Plasma, Urine, Sputum  
Inst Sys Bio, Moritz

Exosomes, Mtb  
proteins by SRM

Serum, Urine  
CSU, Dobos

Ab to Mtb lipids,  
synthetic arrays

Serum  
Alberta, Lowary

Novel Ab class to  
Mtb prot, by elisa

Serum  
Burnet, Anderson

## Protein + sugar

LAM & Mtb prot  
by aptamers

Serum, Urine  
CU, Feldheim

## Protein + lipid

Mtb cell surface  
by Ab magnetic  
beads

Sputum  
Rutgers, Alland

## Lipid + metabolite

Mycolic acids &  
metabolites, MS

Serum, Urine, Sputum  
CSU, Belisle

## Volatile organic cmpd

Volatiles in breath  
by Mass Spec

Breath  
Louisville, Graham

# Summary

- **10 projects funded to investigate a wide spectrum of potential biomarkers for diagnosing TB**
  
- **Focus of the program:**
  - Blood and urine as potential samples
  - Protein biomarkers
  - Pathogen biomarkers
  - Variety of detection technologies
  
- **Moving to Phase 2 of the program in Q1 2014 to further validate promising biomarkers and refine/optimize detection**