Biomarkers for Schistosomiasis Associated Morbidity

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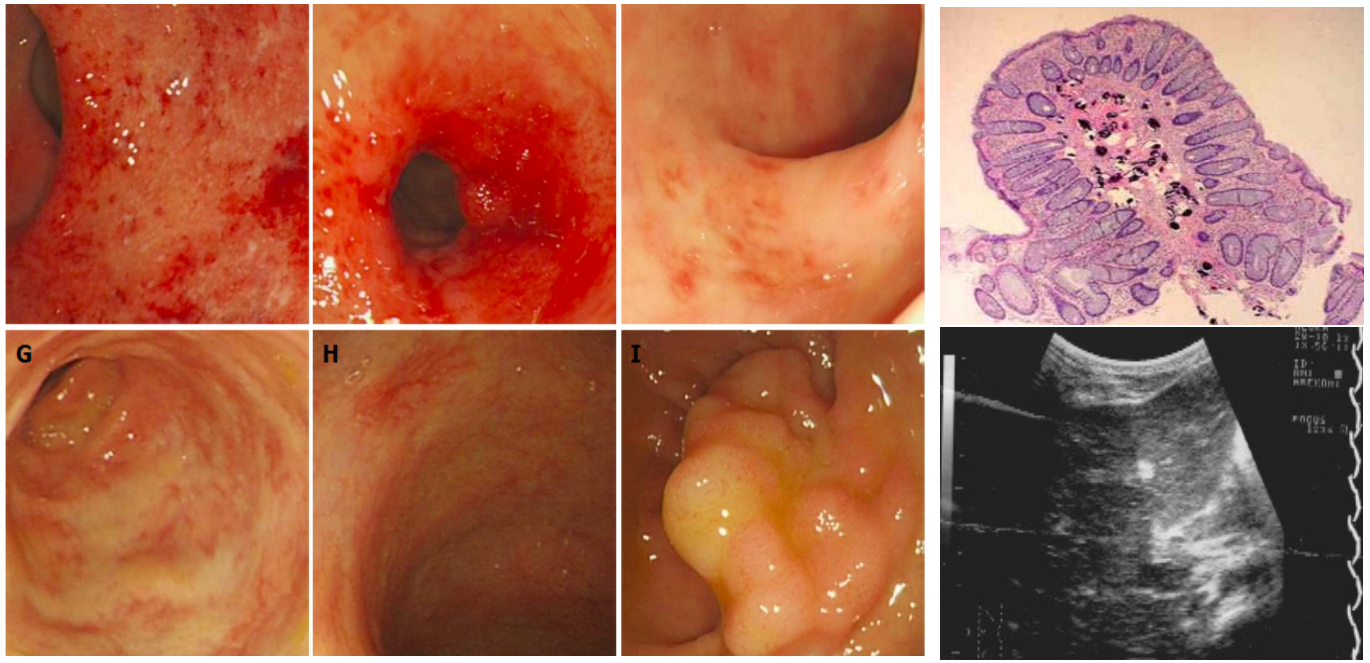
The ‘perfect’ morbidity biomarker

1. **Sensitive**- detect low level morbidity
2. **Specific**- discern between schistosomiasis morbidity and other diseases
3. **Measurable in low invasive samples (urine, stool, blood (DBS), vaginal lavage)**
4. **Responsive to treatment**
5. **Commercially available at the point-of-care- can be used in clinics AND control programmes.**
6. **Low-cost**

Biomarkers for Intestinal Schistosomiasis (*S.mansoni, S.japonicum*)



Biomarkers for *S. mansoni and S.japonicum* morbidities

Anatomical

Intestinal inflammation and occult blood loss

Hepatomegaly

Splenomegaly/hypersplenism

Hepatic fibrosis

Portal vein hypertension

Intestinal hemorrhage

Functional

More Acute

Small intestinal dysfunction

Chronic pain

Anemia

Exercise intolerance

Reduced emotional QoL

Poor school behavior and performance

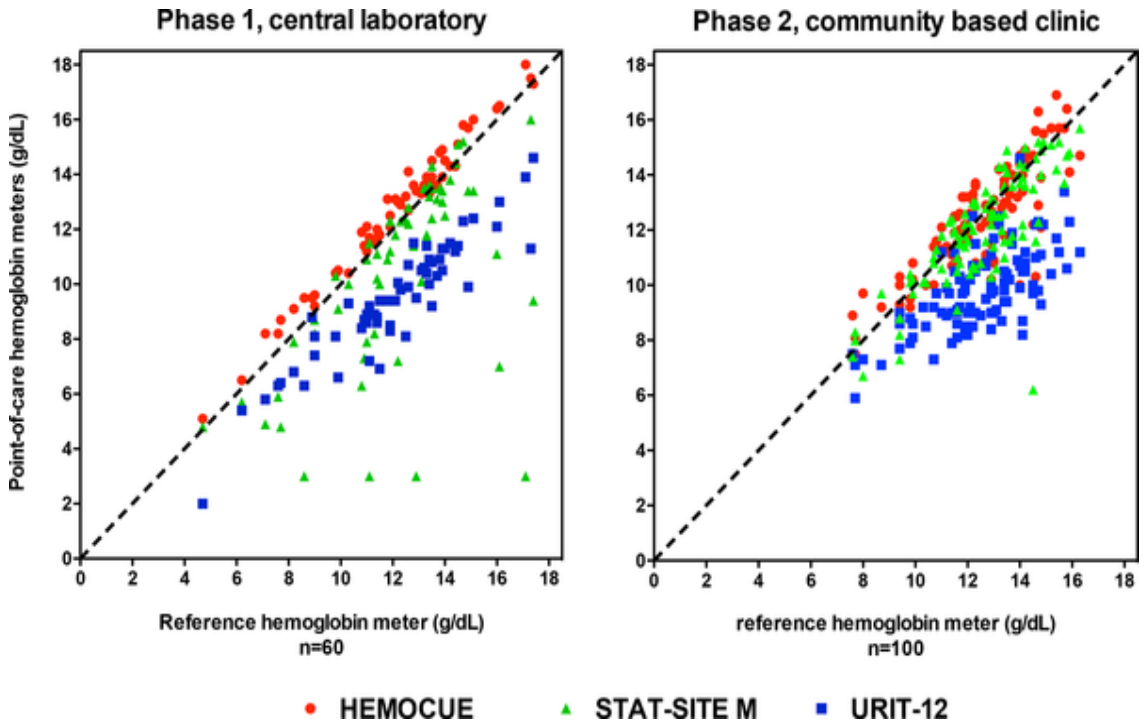
Growth

Loss of earnings

Death

More Chronic

Anemia- detection of Hb



Jaggernath M et al (2016) PLoS ONE

1. Sensitive-
2. Specific-
3. Measurable in low blood volume
4. Responsive to treatment
5. Commercially available at the point-of-care
6. Low-cost

Biomarkers for Intestinal inflammation and occult blood loss

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Fecal Occult Blood and Fecal Calprotectin as Point-of-Care Markers of Intestinal Morbidity in Ugandan Children with *Schistosoma mansoni* Infection

Amaya L. Bustinduy[1]*, José C. Sousa-Figueiredo[1,2], Moses Adriko[3], Martha Betson[4], Alan Fenwick[5], Narcis Kabatereine[3], J. Russell Stothard[1]

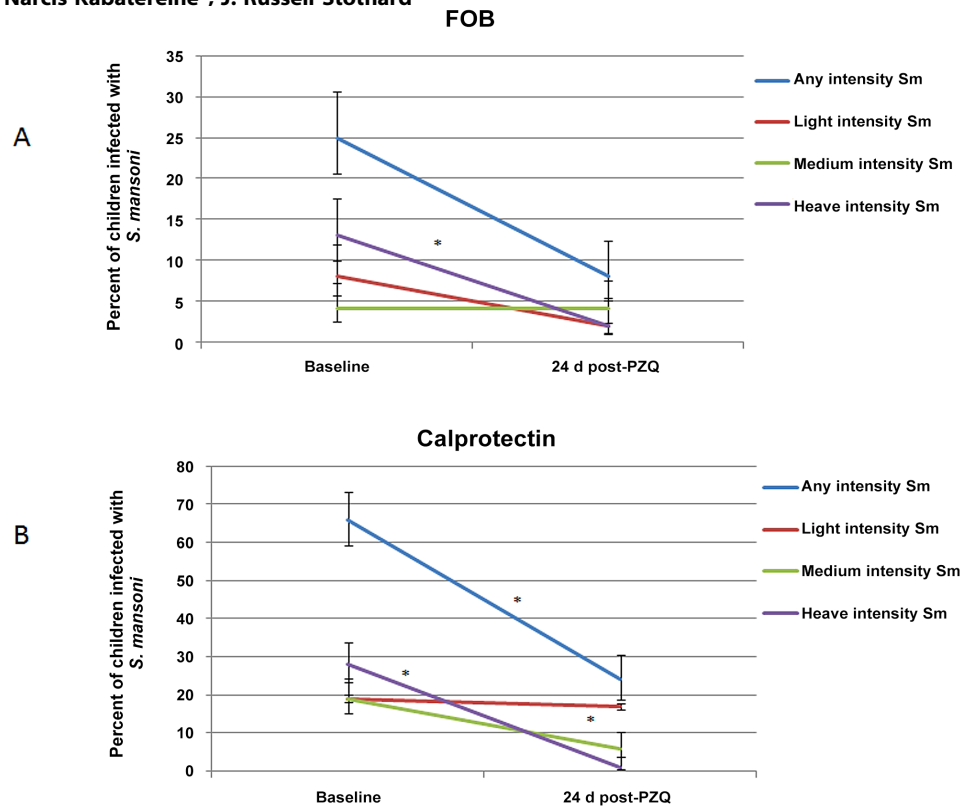


Figure 3. Percent of children egg positive for *S. mansoni* with positive FOB (A) and calprotectin (B) at baseline and 24 days after PZQ treatment. Statistically significant values are indicated *.

doi:10.1371/journal.pntd.0002542.g003

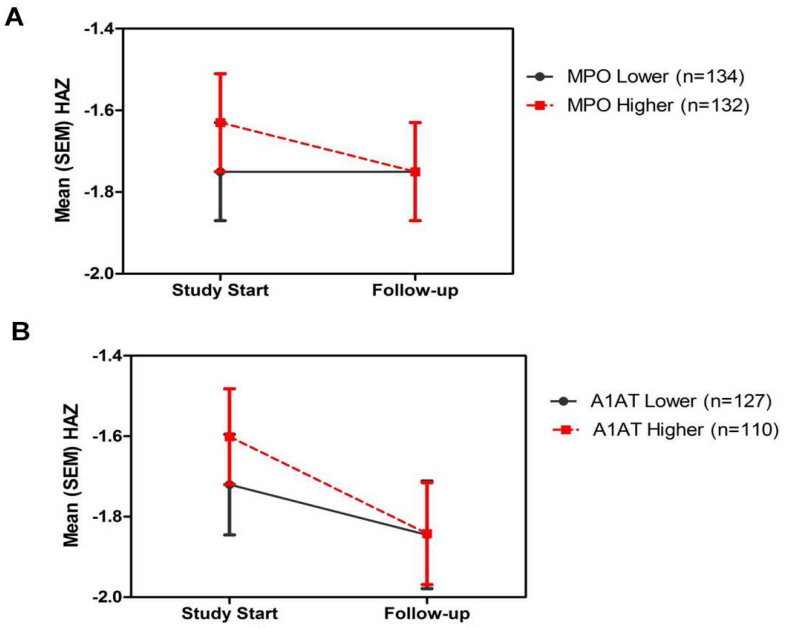
1. Sensitive- ↑↑
2. Specific- ↓↓
3. Measurable in stool ↑↑↑
4. Responsive to treatment ↑↑↑
5. Commercially available at the point-of-care ↑↑↑
6. Low-cost
   1. FOB ↑↑
   2. Calprotectin ↓↓

Small intestinal morbidity biomarkers leading to poor linear growth

PLOS ONE | RESEARCH ARTICLE

Biomarkers of Environmental Enteropathy, Inflammation, Stunting, and Impaired Growth in Children in Northeast Brazil

Richard L. Guerrant[1]*, Alvaro M. Leite[2], Relana Pinkerton[1], Pedro H. Q. S. Medeiros[2], Paloma A. Cavalcante[2], Mark DeBoer[1], Margaret Kosek[8], Christopher Duggan[3], ...vann[6], ...rie M. Guedes[7], ...e Moura ...eon[5],



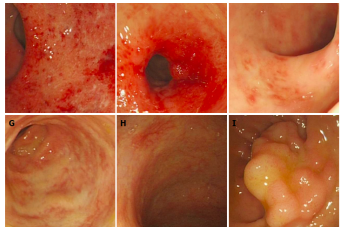
Assessment of Environmental Enteric Dysfunction in the SHINE Trial: Methods and Challenges

Andrew J. Prendergast,[1,2,3] Jean H. Humphrey,[1,3] Kuda Mutasa,[1] Florence D. Majo,[1] Sandra Rukobo,[1] Margaret Govha,[1] Mduduzi N. N. Mbuya,[1,3,4] Lawrence H. Moulton,[3] and Rebecca J. Stoltzfus[4]; for the Sanitation Hygiene Infant Nutrition Efficacy (SHINE) Trial Team[a]

Results form the MALED study (Gates, NIH)

- **Microbial Translocation and systemic inflammation**: Plasma LPS (endotoxin), EndoCAb, IL-6, CRP,alfa-1 acid glycoprotein
- **Barrier disruption (permeability)** : Urine Lactose/Mannose ratio, Stool Regenerating gene 1B (REG-1B), (Intestinal fatty acid binding protein (I-FABP)
- **Intestinal Inflammation**: Stool Myeloperoxidase (MPO) and neopterin, Stool Alfa-1 antitripsine

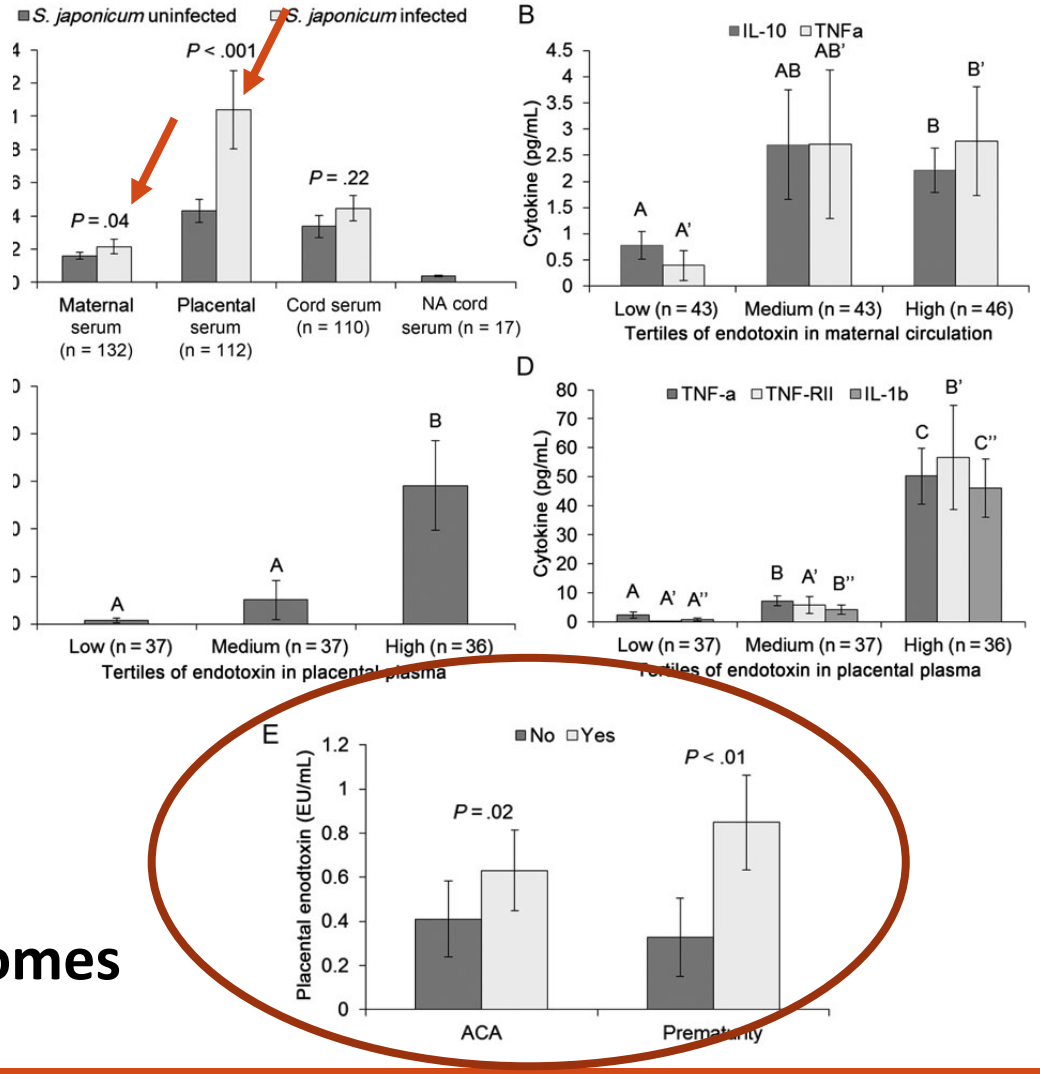
Small intestinal morbidity biomarkers leading to poor growth; What about schistosomiasis?



BRIEF REPORT

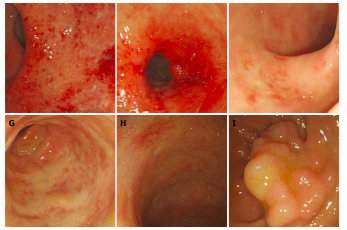
Schistosomiasis Japonica During Pregnancy Is Associated With Elevated Endotoxin Levels in Maternal and Placental Compartments

Emily A. McDonald,[1,2] Sunthorn Pond-Tor,[1] Blanca Jarilla,[3] Marianne J. Sagliba,[3] Annaliza Gonzal,[3] Amabelle J. Amoylen,[3] Remigio Olveda,[3] Luz Acosta,[1,3] Fusun Gundogan,[4] Lisa M. Ganley-Leal,[1,5] Jonathan D. Kurtis,[1,2] and Jennifer F. Friedman[1,5]



Poor neonatal outcomes

Small intestinal morbidity biomarkers leading to poor growth; What about schistosomiasis?



BRIEF R

Schistoso
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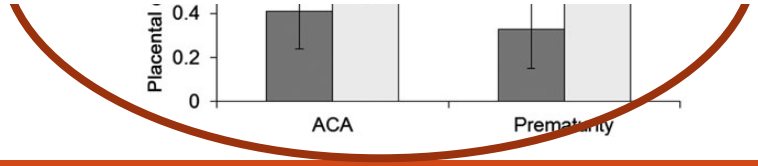
Compartı

Emily A. McDonald
Marianne J. Saglib
Remigio Olveda,[3] L
Jonathan D. Kurtis,

1. Sensitive-
2. Specific-
3. Measurable in urine or stool
4. Responsive to treatment-
5. Commercially available at the point-of-care
6. Low-cost

Poor neonatal outcomes



Biomarkers of liver fibrosis

Periportal Fibrosis in Human *Schistosoma mansoni* Infection Is Associated with Low IL-10, Low IFN-γ, High TNF-α, or Low RANTES, Depending on Age and Gender[1]

Mark Booth,[2]* Joseph K. Mwatha,[†] Sarah Joseph,* Frances M. Jones,* Hilda Kadzo,[‡] Edmund Ireri,[†] Frances Kazibwe,[§] Jovanice Kemijumbi,[3§] Curtis Kariuki,[¶] Gachuhi Kimani,[†] John H. Ouma,[†] Narcis B. Kabatereine,[§] Birgitte J. Vennervald,[‖] and David W. Dunne*

PLOS | NEGLECTED TROPICAL DISEASES

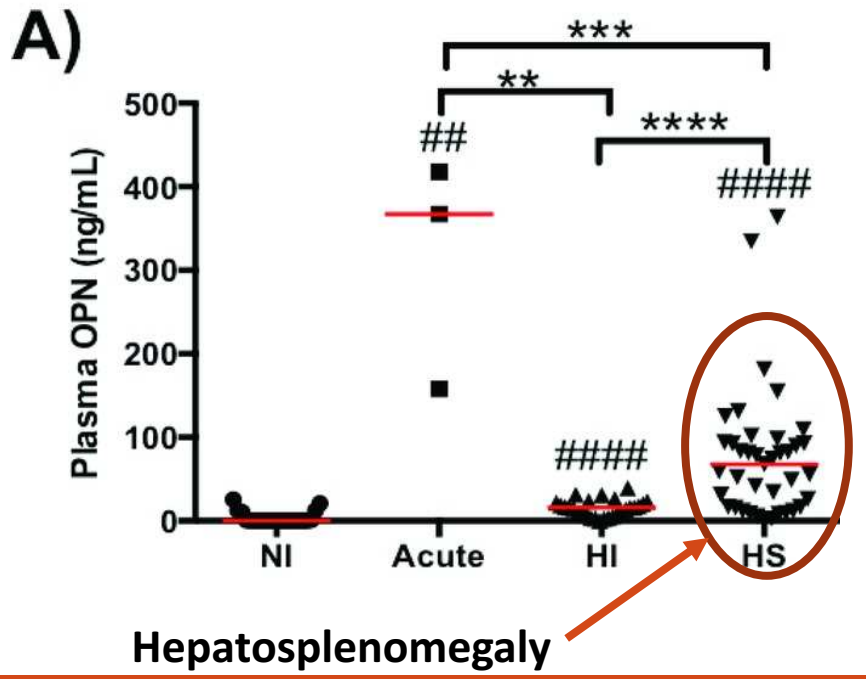
RESEARCH ARTICLE

Osteopontin Is Upregulated in Human and Murine Acute Schistosomiasis Mansoni

Thiago Almeida Pereira[1,2,3,4], Wing-Kin Syn[5,6,7], Frederico Figueiredo Amâncio[2], Pedro Henrique Diniz Cunha[2], Julia Fonseca Morais Caporali[2], Guilherme Vaz de Melo Trindade[2,8], Elisângela Trindade Santos[3], Márcia Maria Souza[3], Zilton Araújo Andrade[3], Rafal P Witek[9], William Evan Secor[10], Fausto Edmundo Lima Pereira[11], José Roberto Lambertucci[2‡]*, Anna Mae Diehl[1‡]*

Th2 Cytokines Are Associated with Persistent Hepatic Fibrosis in Human *Schistosoma japonicum* Infection

H. M. Coutinho,[1,3] L. P. Acosta,[7] H. W. Wu,[1] S. T. McGarvey,[2,3] L. Su,[4] G. C. Langdon,[1] M. A. Jiz,[7] B. Jarilla,[7] R. M. Olveda,[7] J. F. Friedman,[1,5] and J. D. Kurtis[1,6]



Biomarkers of liver fibrosis

Periportal Fibrosis in Huma
Associated with Low IL-10,
RANTES, Depending on Ag

Mark Booth,[2]* Joseph K. Mwatha,[†] Saral
Edmund Ireri,[†] Frances Kazibwe,[§] Jovani
John H. Ouma,[†] Narcis B. Kabatereine,[§] I

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Osteopontin Is Upre
Murine Acute Schist

Thiago Almeida Pereira[1,2,3,4], Wing-Kin
Henrique Diniz Cunha[2], Julia Fonseca
Melo Trindade[2,8], Elisângela Trindade
Araújo Andrade[3], Rafal P Witek[9], Willia
José Roberto Lambertucci[2‡]*, Anna M

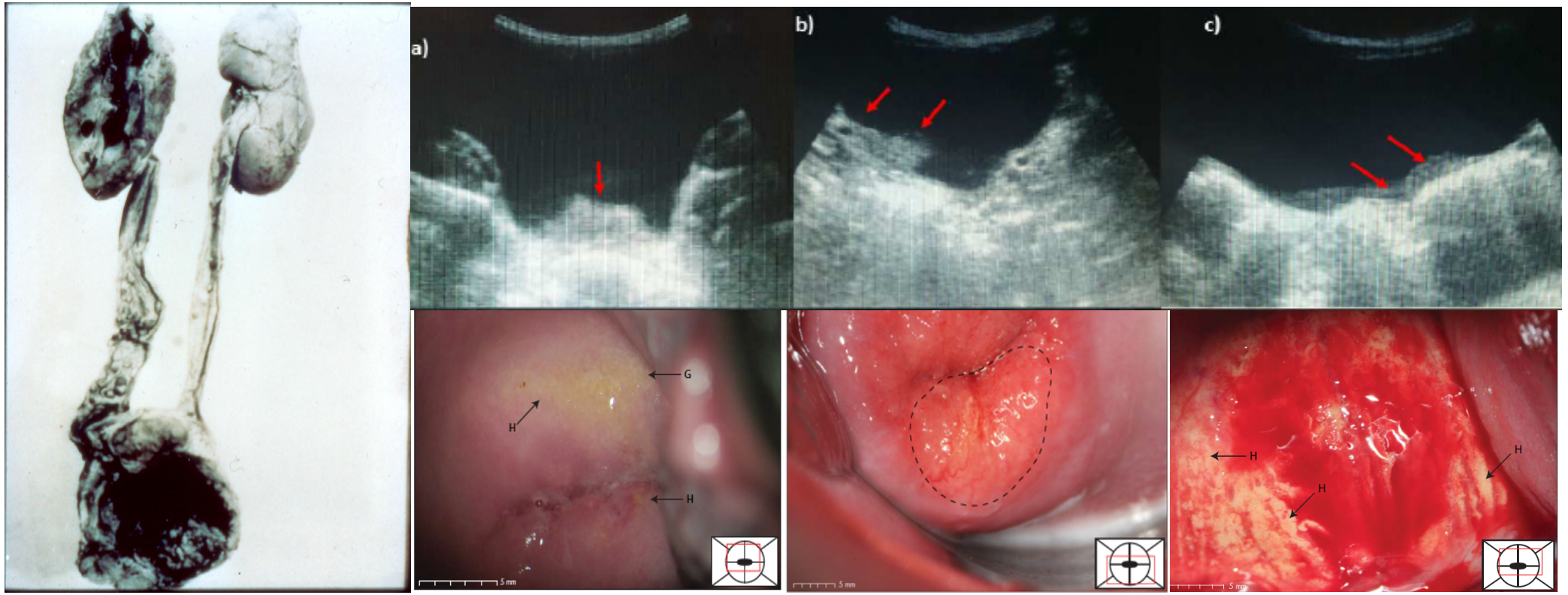
1. Sensitive-↑↑
2. Specific-↓↓
3. Measurable in DBS↓
4. Responsive to treatment-↑
5. Commercially available at the point-of-care ↓↓
6. Low-cost↓↓

Persistent Hepatic
ponicum Infection

angdon,[1] M. A. Jiz,[7] B. Jarilla,[7]

Hepatosplenomegaly

Biomarkers for Urogenital Schistosomiasis (*S.haematobium*)



Biomarkers for *S. haematobium* morbidities

Anatomical

Urinary tract bleeding and protein loss

Cystitis, ureteritis

Bladder polyposis

Genital inflammation and contact bleeding

Female Genital lesions (sandy patches, rubbery papules)

Hydroureter, hydronephrosis

Secondary infection

Bladder cancer

Functional

Dysuria, dyspareunia

Anemia

Sub-fecundity

Exercise intolerance

Reduced QoL

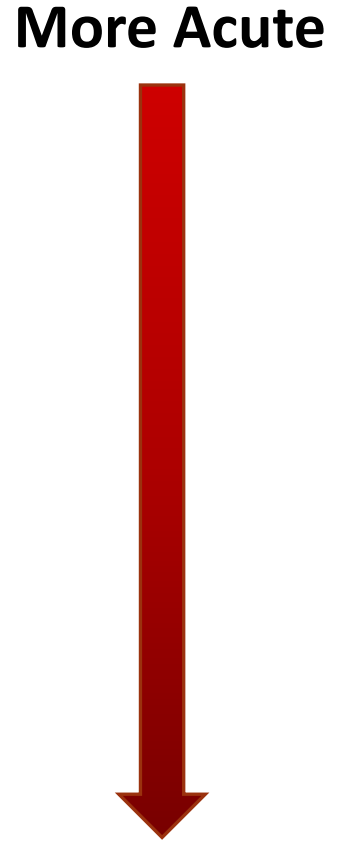
Stunting

Cognitive impairment

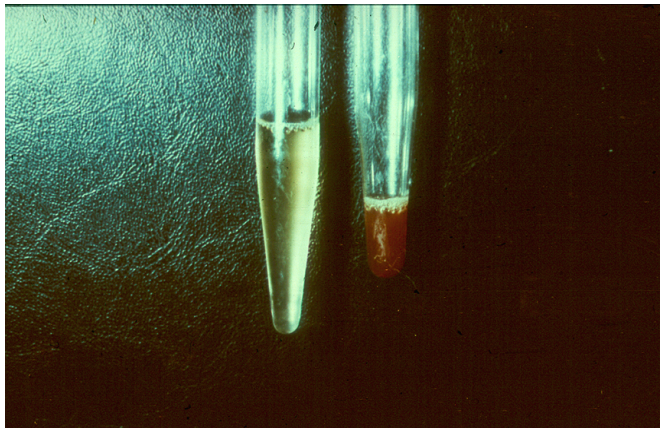
Poor school performance

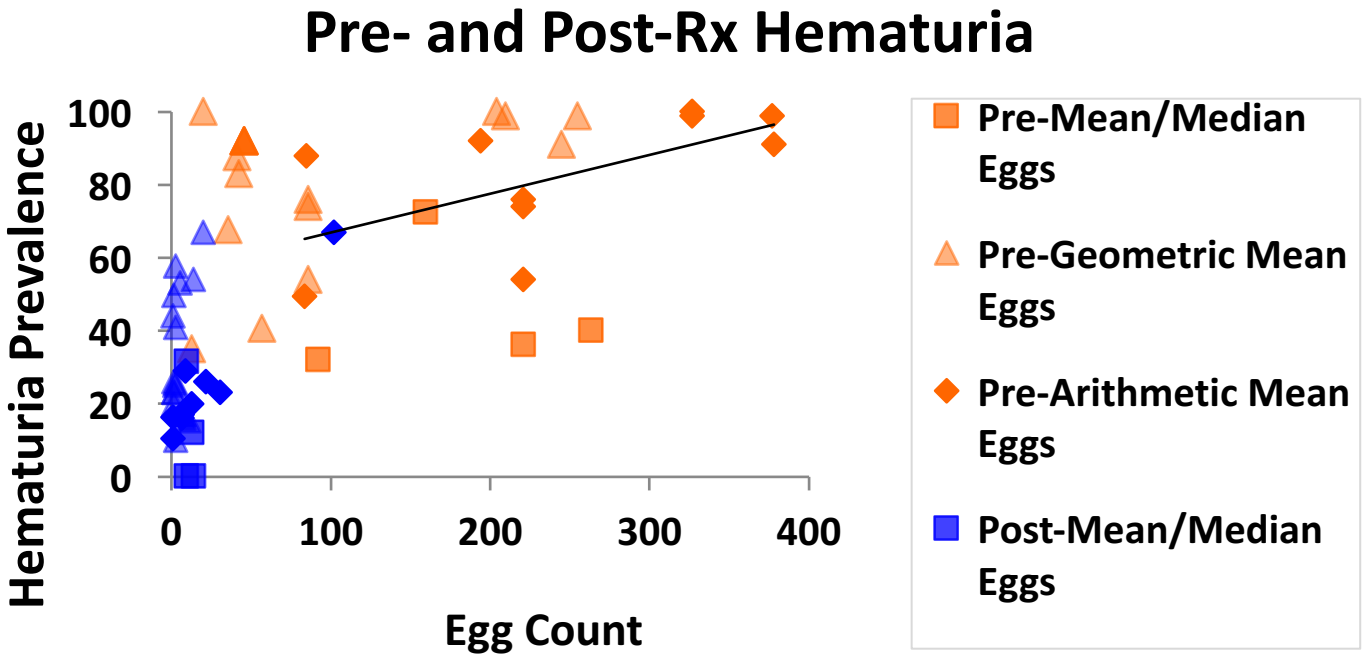
Loss of earnings

Death



MORBIDITY DUE TO INFLAMMATION (Urinary tract)

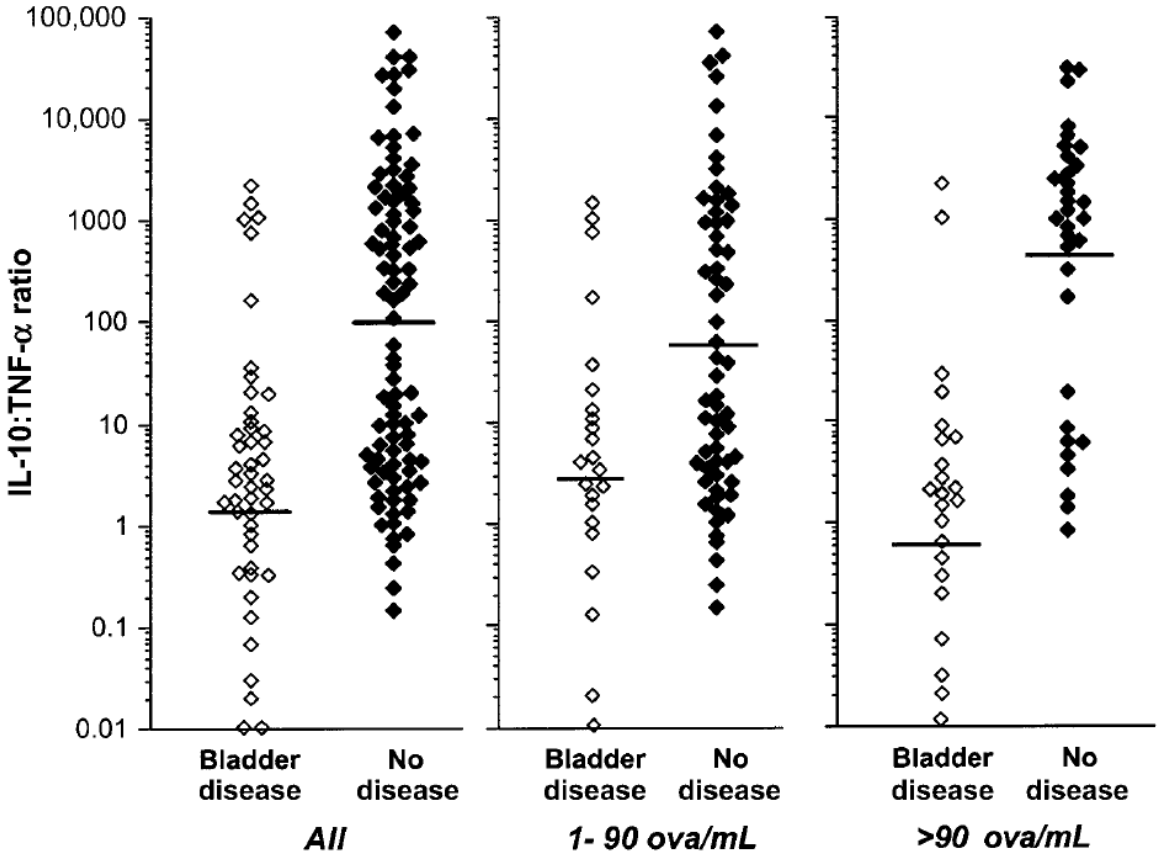




1. Sensitive- ↑↑
2. Specific- ↓
3. Measurable in urine ↑↑↑
4. Responsive to treatment- ↑↑↑
5. Commercially available at the point-of-care ↑↑↑
6. Low-cost ↑↑

Data from Andrade, et al., PLOS NTDs 2017

IMMUNE BIOMARKERS OF BLADDER DISEASE



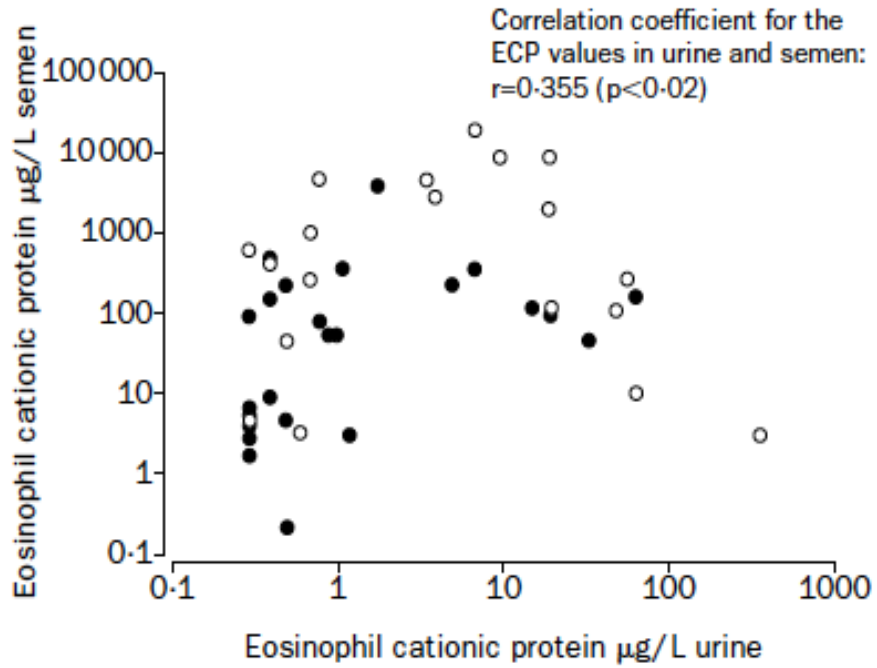
The IL-10 to TNF balance determines the likelihood of disease

1. Sensitive- ↑↑↑
2. Specific- ↓
3. Measurable in DBS ↓↓↓
4. Responsive to treatment- ↑↑
5. Commercially available at the point-of-care ↓↓↓
6. Low-cost ↓↓

Wamachi, et al., J Infect Dis 2004

Biomarkers for male genital schistosomiasis

1. Sensitive- ↑↑↑
2. Specific- ↓
3. Measurable in semen and urine ↑↑↑
4. Responsive to treatment- ??
5. Commercial/point-of-care- ↓↓↓
6. Low-cost ↓



Correlations with MGS

- SEA and ECP in semen
- CAA in plasma

Leutcher et al, Lancet 2000
Leutcher et al, AJTMH, 2008

Biomarkers for Female Genital Schistosomiasis

FGS lesions

Inflammation
Mucosal friability

Increased HIV Acquisition
Poor Reproductive Health

- ECP

- CD14
- CD4 CCR5 +

Pro-inflammatory cytokines ?

- Correlation with CAA ? (BILHIV study in Zambia)

???

- 30 % correlation with Urine egg detection
- 67% stivity/ 83 % spp of *Sh* PCR in Vaginal lavage

Clinical staging
Clinical monitoring
Response to treatment

Kjetland et al, AJTMH, 2009 ;Kleppa et al, PlosOne,2014, Midzi et al, Parasite Imm, 2003

Biomarkers for Female Genital Schistosomiasis

FGS lesions → **Inflammation Mucosal friability** → **Increased HIV Acquisition Poor Reproductive Health**

1. Sensitive- ↑
2. Specific- ↓
3. Measurable in genital sample ↑
4. Responsive to treatment- ↑
5. Commercial/point-of-care- ↓↓↓
6. Low-cost ↓↓↓

- ECP
- y cytokines ?
- 30 % corre
- 67% stivity, … staging
- lavage

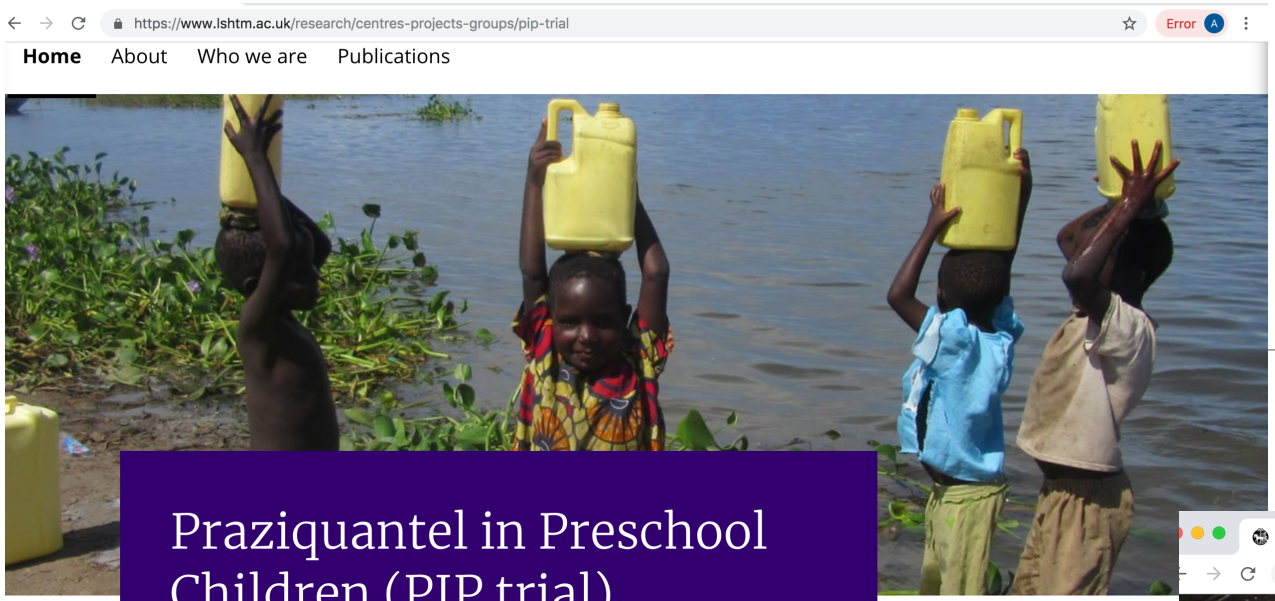
Clinical monitoring
Response to treatment

Kjetland et al, AJTMH, 2009 ;Kleppa et al, PlosOne,2014, Midzi et al, Parasite Imm, 2003

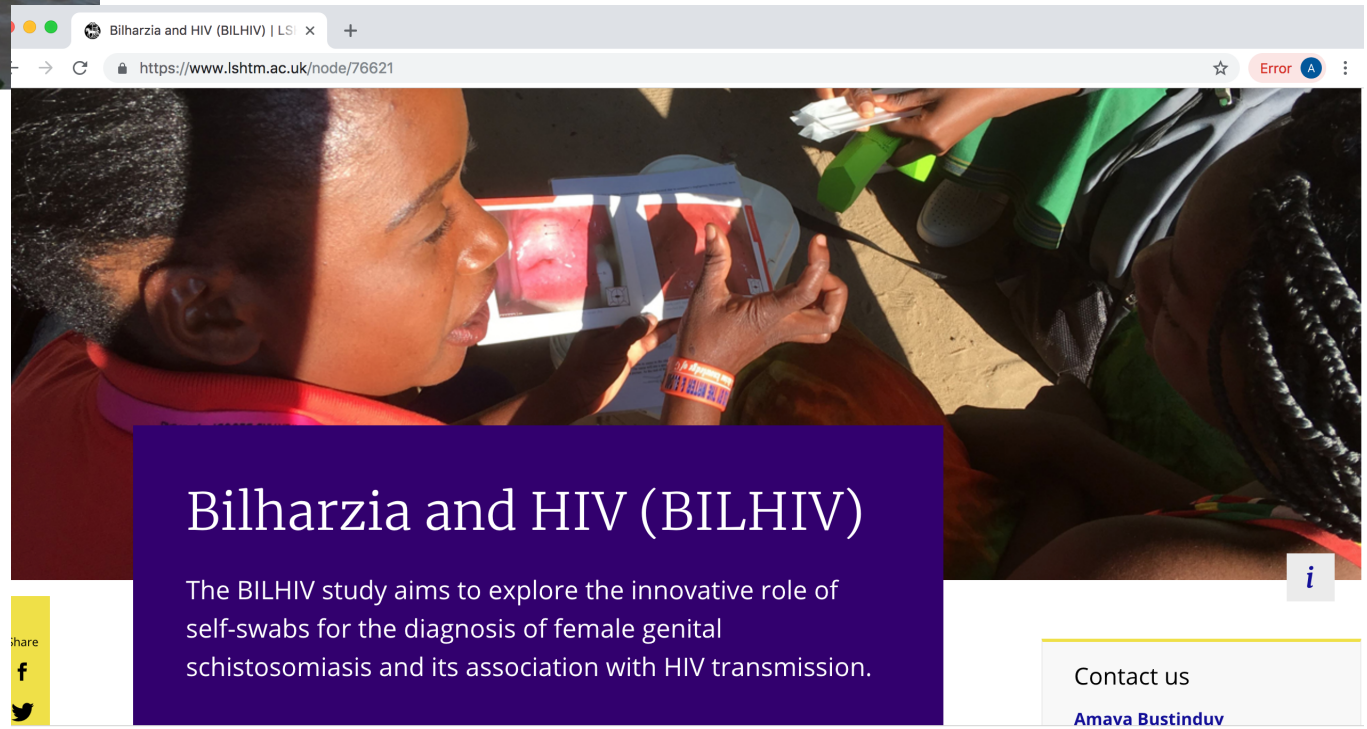
SUMMARY

- There is no 'perfect' biomarker, it all depends on where it needs to perform (control programmes vs clinical practice)
- Good to aim for a biomarker that could be a **morbidity** test-of-cure (different from infection!)
- Hemacue is a winner for all types of schistosomiasis
- **Intestinal schistosomiasis**
  1. Hb, FOB, Calprotectin
  2. LPS, MOP, Neopterin, EndoCAb, IL-6, CRP,alfa-1 acid glycoprotein, Urine Lactose/Mannose ratio, Stool REG-1B, I-FABP,Stool Alfa-1 antitripsine
  3. Liver fibrosis markers- research context
- **Urogenital schistosomiasis**
  1. Hemastick
  2. **NEEDS URGENT RESEARCH** to find MGS and FGS good and affordable markers of disease from genital samples

Thank you!



https://www.lshtm.ac.uk/research/centres-projects-groups/pip-trial



https://www.lshtm.ac.uk/node/76621