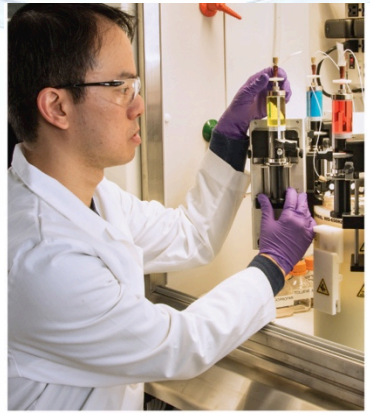
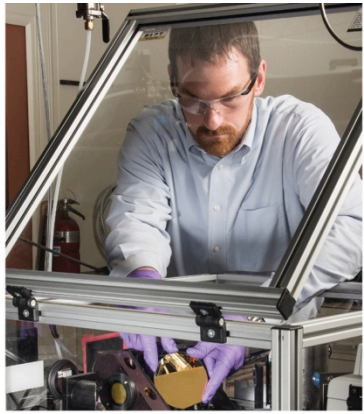
Microbiome and Metagenomic Standards





- **Scott Jackson**
- **Leader, Complex Microbial Systems Group**
- **Biosystems and Biomaterials Division**
- **MML**

MML Microbial Metrology Mission Statement

"To develop advanced measurements that will permit the exploitation of microbes to promote human health, precision medicine and advanced manufacturing"

NIST
National Institute of Standards and Technology
U.S. Department of Commerce

Sept. 19th 2019

MATERIAL MEASUREMENT LABORATORY

2019 NIST Workshop on Standards for Microbiome Measurements

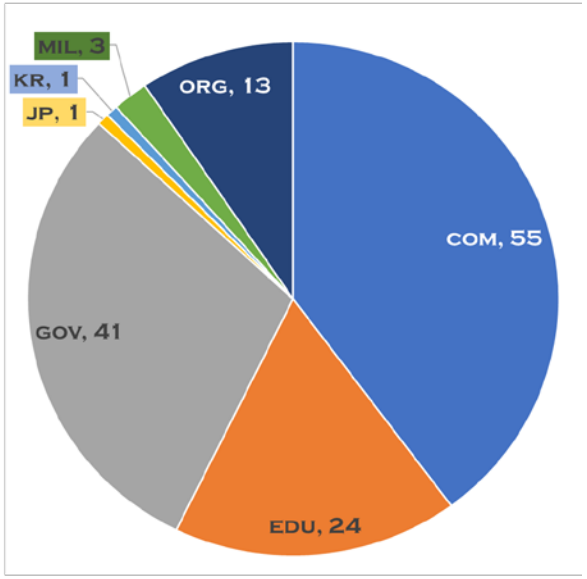
Sept. 9th and 10th 2019

CONFIRMED SPEAKERS

- Eric Lin, NIST Materials Measurement Laboratory
- Freyja Williams, FDA Center for Biologics Evaluation and Research
- Raja Mazumder, George Washington University
- Brittney Goldberg, FDA Center for Devices and Radiological Health
- Jennifer Barb, NIH Center for Information Technology
- Ben Callahan, NC State University
- Elisha Wood-Charlson, Lawrence Berkeley National Lab
- Raul Cano, The Biocollective
- Scott A. Jackson, NIST Biosystems and Biomaterials Division
- Daryl Gohl, University of Minnesota
- Christian C. Abnet, NIH National Cancer Institute
- Ricardo Valladares, Siolta
- Dana Walsh, Rebiotix
- Kit Goldman, USP
- Paul Carlson, FDA/CBER
- Jeffrey Heiser, Boston Analytical
- Jennifer Balkus, University of Washington
- Scott Tighe, University of Vermont
- Dieter Tourlousse, AIST
- Gregory C A Amos, NIBSC
- Phil McQueen, NIH Center for Information Technology

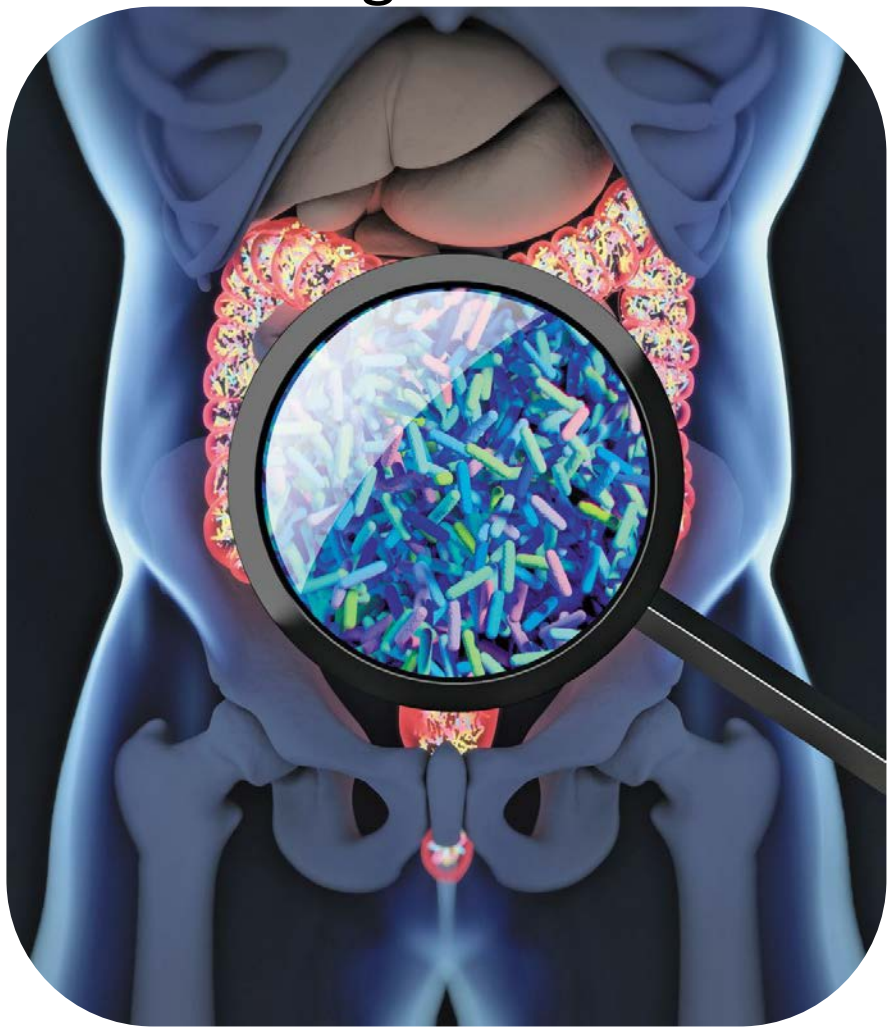
138 Registered Attendees

Who's Here Today?



Clinical Applications of the Human Microbiome

Diagnostics

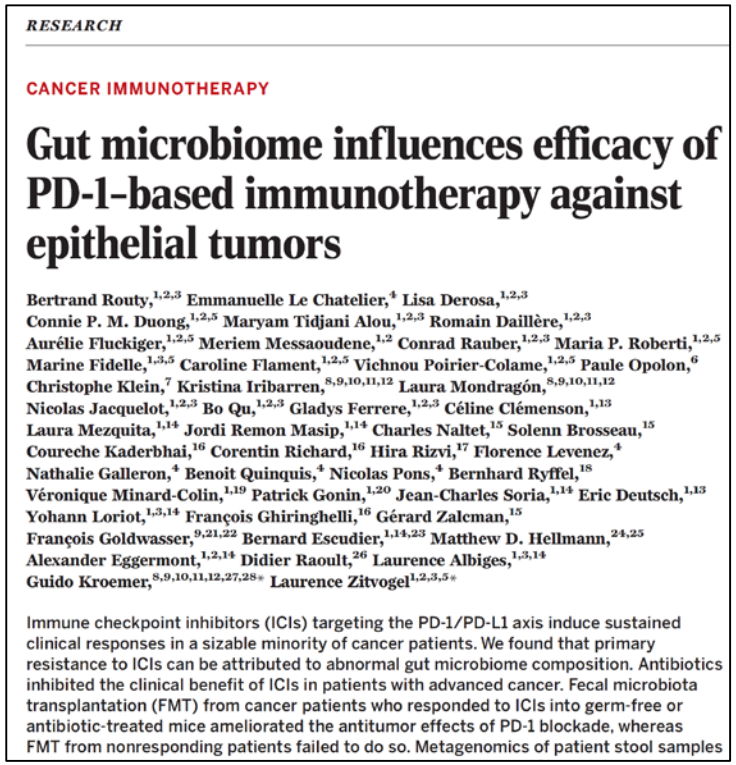


https://www.health.harvard.edu/staying-healthy/do-gut-bacteria-inhibit-weight-loss

Therapeutics

https://www.medicaldaily.com/frozen-capsules-poop-may-help-patients-c-difficile-gut-infections-306792

The Gut Microbiome Modulates Efficacy and Response to Immunotherapy in Cancer Patients



RESEARCH

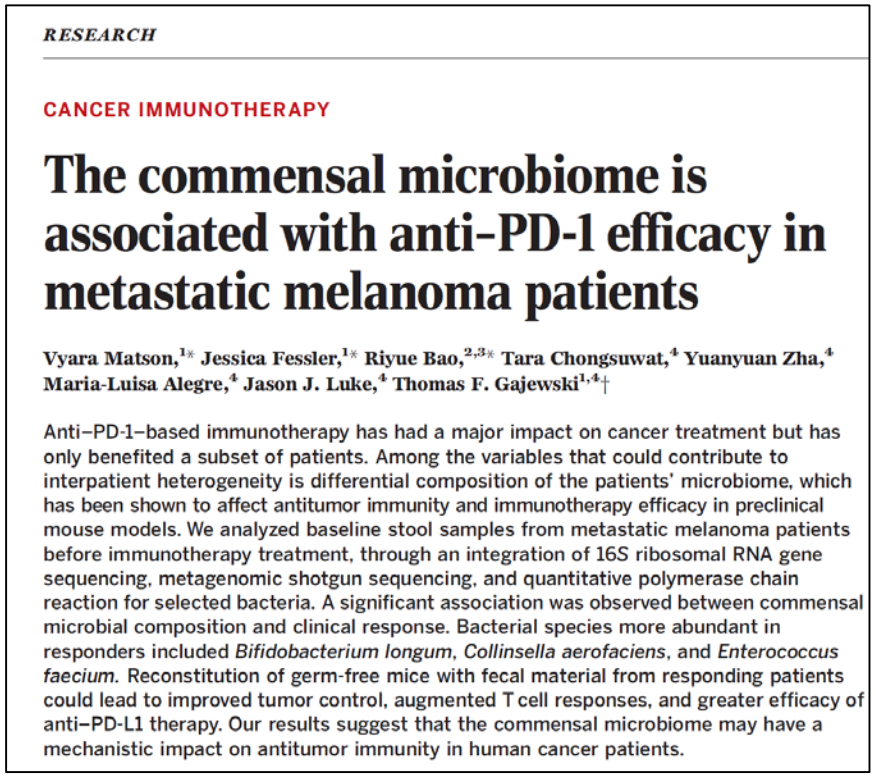
CANCER IMMUNOTHERAPY

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors

Bertrand Routy,[1,2,3] Emmanuelle Le Chatelier,[4] Lisa Derosa,[1,2,3] Connie P. M. Duong,[1,2,5] Maryam Tidjani Alou,[1,2,3] Romain Daillère,[1,2,3] Aurélie Fluckiger,[1,2,5] Meriem Messaoudene,[1,2] Conrad Rauber,[1,2,3] Maria P. Roberti,[1,2,5] Marine Fidelle,[1,3,5] Caroline Flament,[1,2,5] Vichnou Poirier-Colame,[1,2,5] Paule Opolon,[6] Christophe Klein,[7] Kristina Iribarren,[8,9,10,11,12] Laura Mondragón,[8,9,10,11,12] Nicolas Jacquelot,[1,2,3] Bo Qu,[1,2,3] Gladys Ferrere,[1,2,3] Céline Clémenson,[1,13] Laura Mezquita,[1,14] Jordi Remon Masip,[1,14] Charles Naltet,[15] Solenn Brosseau,[15] Coureche Kaderbhai,[16] Corentin Richard,[16] Hira Rizvi,[17] Florence Levenez,[4] Nathalie Galleron,[4] Benoit Quinquis,[4] Nicolas Pons,[4] Bernhard Ryffel,[18] Véronique Minard-Colin,[1,19] Patrick Gonin,[1,20] Jean-Charles Soria,[1,14] Eric Deutsch,[1,13] Yohann Loriot,[1,3,14] François Ghiringhelli,[16] Gérard Zalcman,[15] François Goldwasser,[9,21,22] Bernard Escudier,[1,14,23] Matthew D. Hellmann,[24,25] Alexander Eggermont,[1,2,14] Didier Raoult,[26] Laurence Albiges,[1,3,14] Guido Kroemer,[8,9,10,11,12,27,28*] Laurence Zitvogel[1,2,3,5*]

Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis induce sustained clinical responses in a sizable minority of cancer patients. We found that primary resistance to ICIs can be attributed to abnormal gut microbiome composition. Antibiotics inhibited the clinical benefit of ICIs in patients with advanced cancer. Fecal microbiota transplantation (FMT) from cancer patients who responded to ICIs into germ-free or antibiotic-treated mice ameliorated the antitumor effects of PD-1 blockade, whereas FMT from nonresponding patients failed to do so. Metagenomics of patient stool samples

Routy *et al.*, *Science* **359**, 91–97 (2018) 5 January 2018



RESEARCH

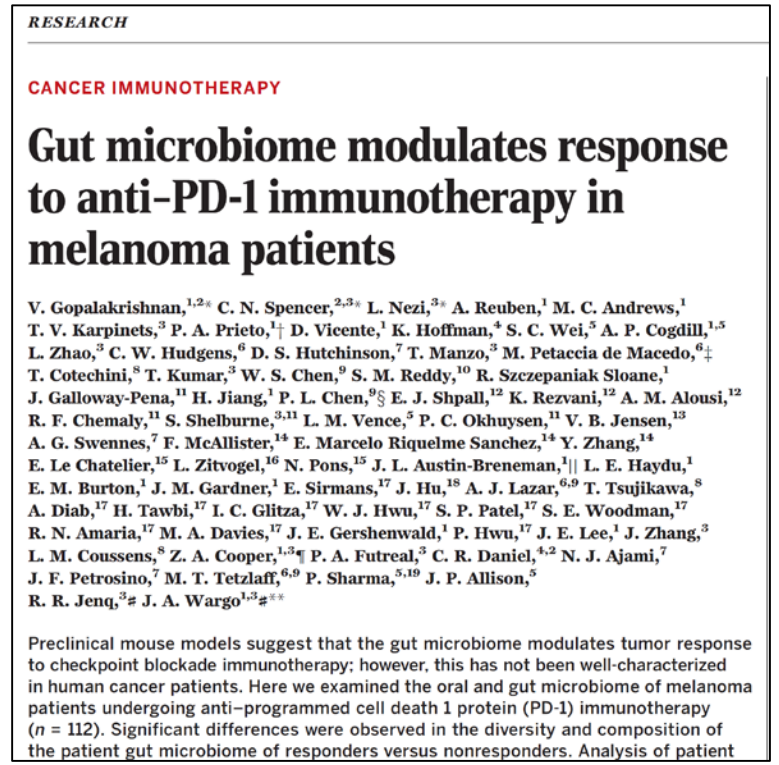
CANCER IMMUNOTHERAPY

The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients

Vyara Matson,[1*] Jessica Fessler,[1*] Riyue Bao,[2,3*] Tara Chongsuwat,[4] Yuanyuan Zha,[4] Maria-Luisa Alegre,[4] Jason J. Luke,[4] Thomas F. Gajewski[1,4†]

Anti–PD-1–based immunotherapy has had a major impact on cancer treatment but has only benefited a subset of patients. Among the variables that could contribute to interpatient heterogeneity is differential composition of the patients' microbiome, which has been shown to affect antitumor immunity and immunotherapy efficacy in preclinical mouse models. We analyzed baseline stool samples from metastatic melanoma patients before immunotherapy treatment, through an integration of 16S ribosomal RNA gene sequencing, metagenomic shotgun sequencing, and quantitative polymerase chain reaction for selected bacteria. A significant association was observed between commensal microbial composition and clinical response. Bacterial species more abundant in responders included *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*. Reconstitution of germ-free mice with fecal material from responding patients could lead to improved tumor control, augmented T cell responses, and greater efficacy of anti–PD-L1 therapy. Our results suggest that the commensal microbiome may have a mechanistic impact on antitumor immunity in human cancer patients.

Matson *et al.*, *Science* **359**, 104–108 (2018) 5 January 2018



RESEARCH

CANCER IMMUNOTHERAPY

Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

V. Gopalakrishnan,[1,2*] C. N. Spencer,[2,3*] L. Nezi,[3*] A. Reuben,[1] M. C. Andrews,[1] T. V. Karpinets,[3] P. A. Prieto,[1†] D. Vicente,[1] K. Hoffman,[4] S. C. Wei,[5] A. P. Cogdill,[1,5] L. Zhao,[3] C. W. Hudgens,[6] D. S. Hutchinson,[7] T. Manzo,[3] M. Petaccia de Macedo,[6‡] T. Cotechini,[8] T. Kumar,[3] W. S. Chen,[9] S. M. Reddy,[10] R. Szczepaniak Sloane,[1] J. Galloway-Pena,[11] H. Jiang,[1] P. L. Chen,[9§] E. J. Shpall,[12] K. Rezvani,[12] A. M. Alousi,[12] R. F. Chemaly,[11] S. Shelburne,[3,11] L. M. Vence,[5] P. C. Okhuysen,[11] V. B. Jensen,[13] A. G. Swennes,[7] F. McAllister,[14] E. Marcelo Riquelme Sanchez,[14] Y. Zhang,[14] E. Le Chatelier,[15] L. Zitvogel,[16] N. Pons,[15] J. L. Austin-Breneman,[1‖] L. E. Haydu,[1] E. M. Burton,[1] J. M. Gardner,[1] E. Sirmans,[17] J. Hu,[18] A. J. Lazar,[6,9] T. Tsujikawa,[8] A. Diab,[17] H. Tawbi,[17] I. C. Glitza,[17] W. J. Hwu,[17] S. P. Patel,[17] S. E. Woodman,[17] R. N. Amaria,[17] M. A. Davies,[17] J. E. Gershenwald,[1] P. Hwu,[17] J. E. Lee,[1] J. Zhang,[3] L. M. Coussens,[8] Z. A. Cooper,[1,3¶] P. A. Futreal,[3] C. R. Daniel,[4,2] N. J. Ajami,[7] J. F. Petrosino,[7] M. T. Tetzlaff,[6,9] P. Sharma,[5,19] J. P. Allison,[5] R. R. Jenq,[3#] J. A. Wargo[1,3#**]

Preclinical mouse models suggest that the gut microbiome modulates tumor response to checkpoint blockade immunotherapy; however, this has not been well-characterized in human cancer patients. Here we examined the oral and gut microbiome of melanoma patients undergoing anti–programmed cell death 1 protein (PD-1) immunotherapy (n = 112). Significant differences were observed in the diversity and composition of the patient gut microbiome of responders versus nonresponders. Analysis of patient

Gopalakrishnan *et al.*, *Science* **359**, 97–103 (2018) 5 January 2018

Bacteria: The next new drug modality

Live Biotherapeutic Products (LBPs)

Rationally-Designed Consortia

- Derived from pure isolates grown in culture
- May contain a single or many strains

Biologically-Derived

- Derived from whole stool
- Highly processed to yield a desired microbial consortia (e.g. spores)

Probiotics ≠ Live Biotherapeutic Products (LBPs)

Dietary Supplement (a food)
Generally Recognized as Safe (GRAS)
Cannot Make Health Claims
Available Off-the-Shelf

Vs.

Live BioTherapeutic Products (LBPs)
Regulated as a “drug”
Demonstrated safety and efficacy via clinical trials
Prescribed by a physician

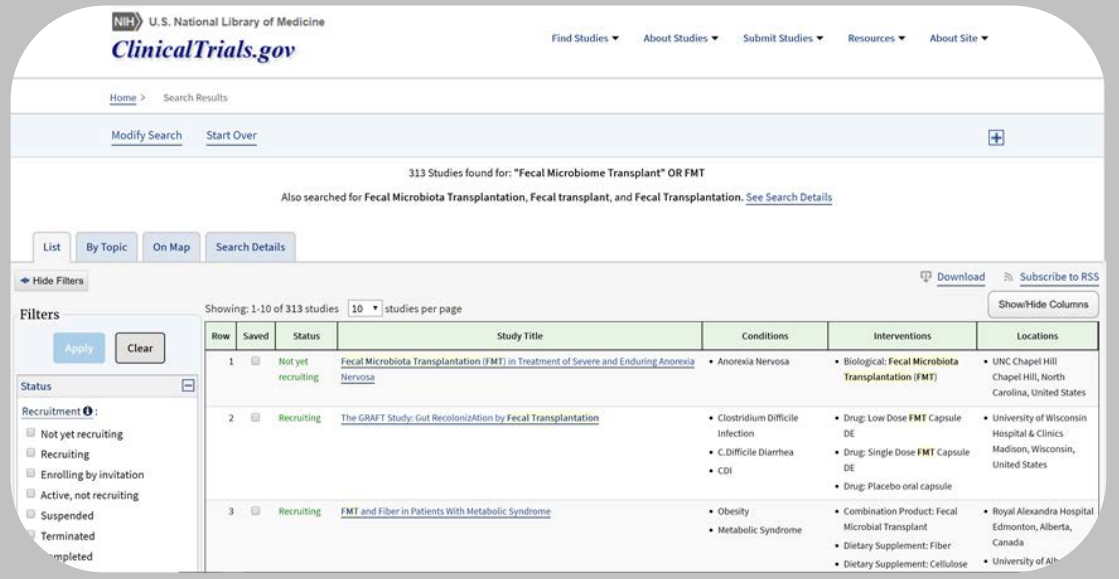
http://thescienceexplorer.com/brain-and-body/scientists-plan-use-freeze-dried-poop-pills-help-people-lose-weight

Fecal Microbiome Transplants (FMTs)

ClinicalTrials.gov reports 149 FMT trials are active or recruiting as 0f 09/08/19 and include:

- Bipolar Disorder
- Tourette's Syndrome
- Parkinson's Disease
- Modulate Efficacy of Immunotherapy in Cancer Patients
- Alcohol Misuse in Cirrhosis
- Treatment of Obesity
- Treatment of IBD and CDI
- Multidrug Resistant Organism Reversal
- Etc. etc.

Reported Efficacy of 60%-90% for Recurring and Primary *Clostridium difficile* Infection



Chemistry, Manufacturing, and Control (CMCs) for LBPs

Requires the Development and Validation of Analytical Methods that are Reproducible to Measure:

1) Identity
2) Purity
3) Potency
4) Stability
5) Antibiotic Resistance

The identity of each microbial strain present in the drug substance should be determined using a specific and reproducible assay.

- Testing may be based upon biochemical methods such as fermentation profile or genotypic methods, including such as ribotyping, restriction fragment length polymorphism (RFLP), or both.
- In addition, if one or more genetic loci, either naturally occurring or engineered, have been identified as critical for biological activity, we recommend that you develop a specific identity assay.

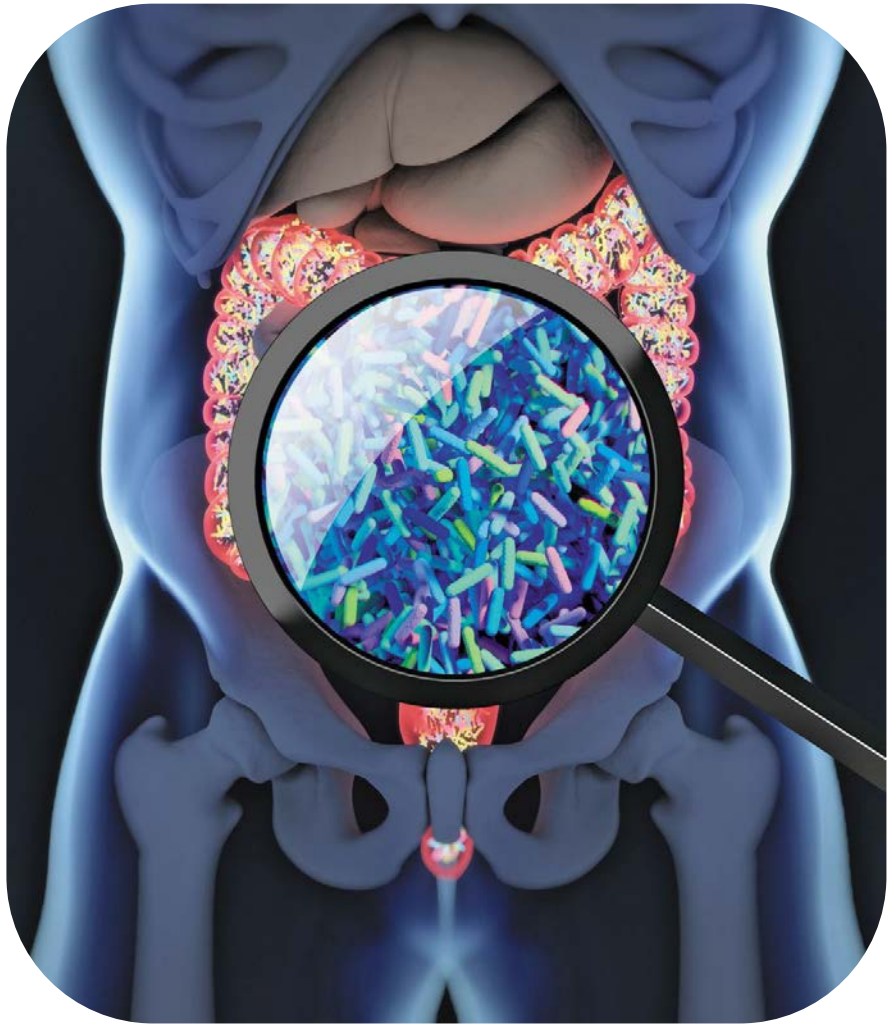
Potency of live microbial products is generally a measure of viable cells per unit or dose, i.e., colony-forming units (CFUs).

- Additional measures of product potency may be applicable, depending on the specific product strain(s) and knowledge of the mechanism(s) of action.

Purity tests of a LBP may include assessment of endotoxin content, residual antibiotics, and/or the quantification of residual toxic components or contaminants introduced during manufacture.

- LBPs may need to be devoid of any extraneous organisms, or alternatively should have a low level of extraneous organisms.
- Tests for microbial bioburden should be in accordance with the US Pharmacopeia (39 USP <61>) Microbiological Examination of Nonsterile Products: Microbial
- Enumeration Tests (Ref. 6). Depending on the nature of other products campaigned at the manufacturing facility and the proposed use of the product, the inclusion of tests specific for other organisms may be necessary

Clinical Microbiome Measurements and Emerging Microbiome Diagnostics

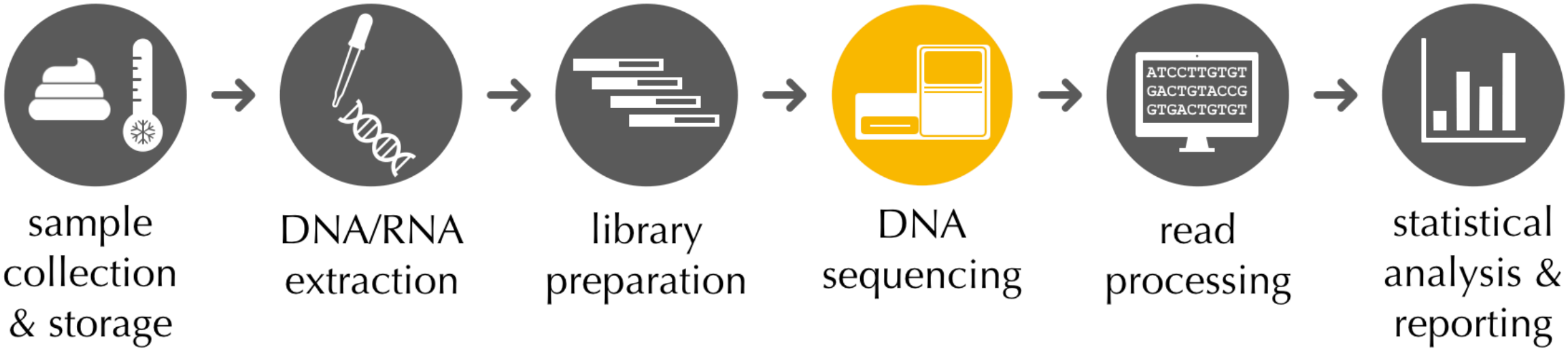


https://www.health.harvard.edu/staying-healthy/do-gut-bacteria-inhibit-weight-loss

Clinical Metagenomic Microbiome Measurements

1. Monitoring engraftment of strains following administration of a LBP. PK/PD
2. Screening patients before a therapeutic intervention (e.g. immunotherapy) to find correlations between treatment outcome and their microbiome profile
3. Epidemiological studies designed to understand the role of the microbiome in disease risk
4. Measuring donor FMT material before administration to identify microbiome signatures that are indicators of efficacy
5. Diagnosing disease or predisposition to disease

Metagenomic Measurement Workflow



Bias in Microbiome-Metagenomic Measurements

Guest post by Tina Hesman Saey

"I asked two different companies to analyze my gut microbiome. ***American Gut (left) gave nearly opposite results to those from uBiome*** *(right) with respect to the major phyla of bacteria in a duplicate sample."*

Rashmi Singha, an epidemiologist at the National Cancer Institute stated: ***"The lack of reproducibility between studies was frustrating. To me it seemed like cowboy country. It needed to have some kind of order."***

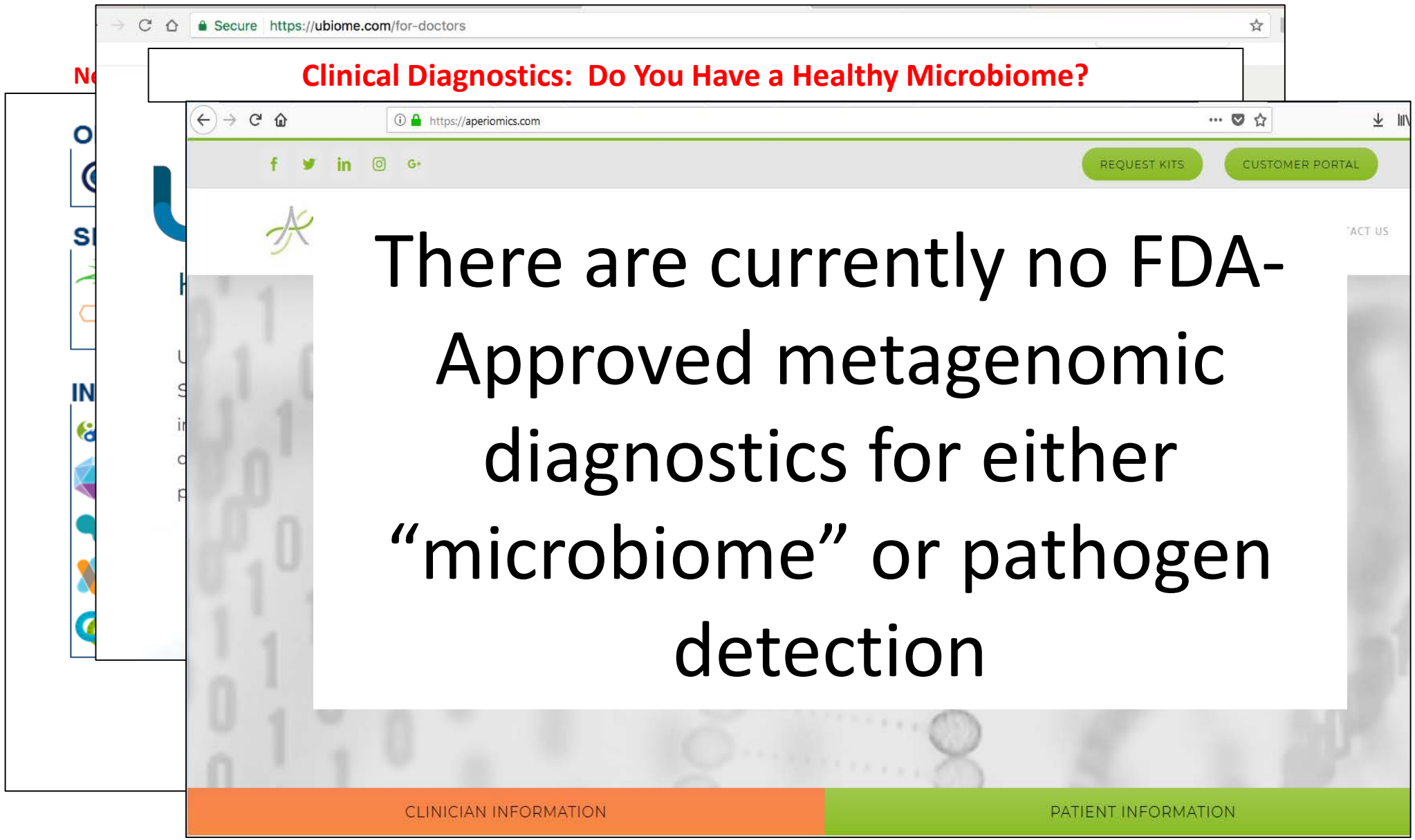
"Another blogger, who is ***a bioinformatician, got different results than American Gut reported to him when he used his own software to analyze their raw data."***

"But DNA extraction is not the only thing that could go wrong. It seems ***that every step of the process — from how you collect the sample through the computer programs used to analyze the DNA data — is a potential culprit****."*

Or as Knight puts it, ***"All sorts of unlikely things are possible, and finding out which one is true is difficult."***

"The point is, ***scientists are trying to find ways to standardize microbiome studies so that they can directly compare results. They don't yet have the answers,*** *but they will take the first steps toward figuring it out at a workshop this fall."*

An Entire (Bio)Industry Build Around Metagenomic Measurements



Broad Applications of Metagenomics

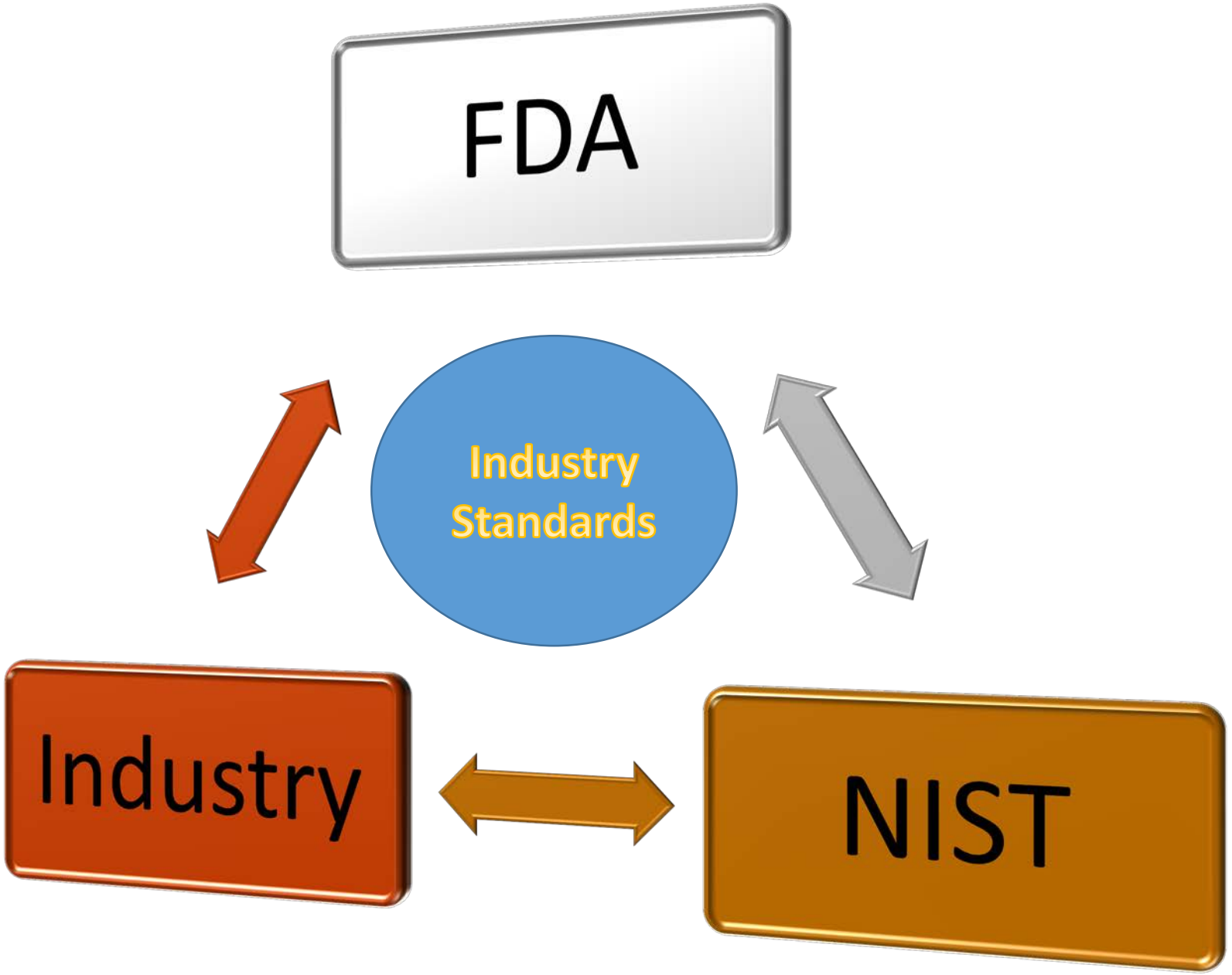
Infectious Disease Diagnostics

RMTM in Biomanufacturing

Food Safety

Counter-Bioterrorism

Human Microbiome


FDA
Industry Standards
Industry
NIST

FDA calls on NIST for Microbial Standards

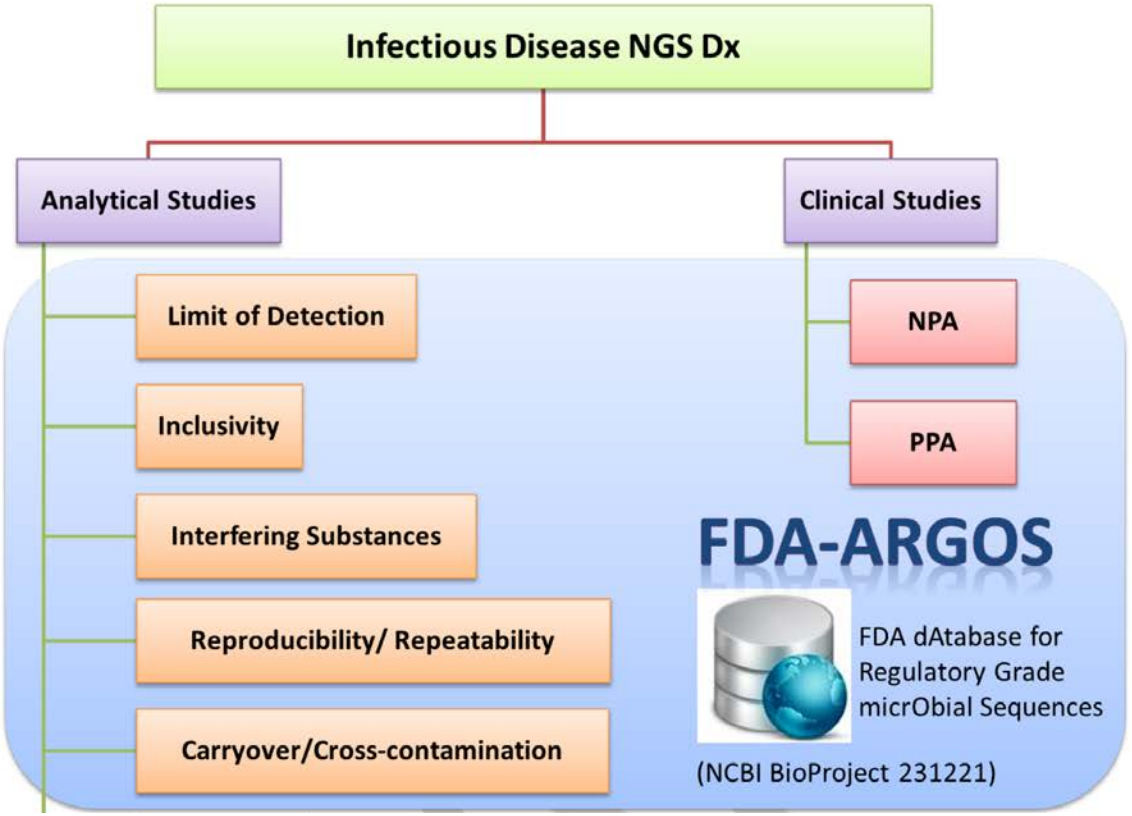
Infectious Disease Next Generation Sequencing Based Diagnostic Devices: Microbial Identification and Detection of Antimicrobial Resistance and Virulence Markers

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

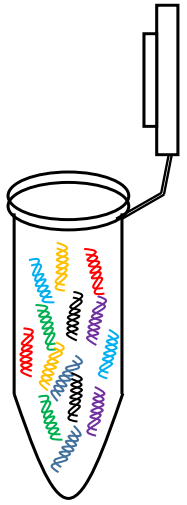
This draft guidance document is being distributed for comment purposes only.

Document issued on: May 13, 2016



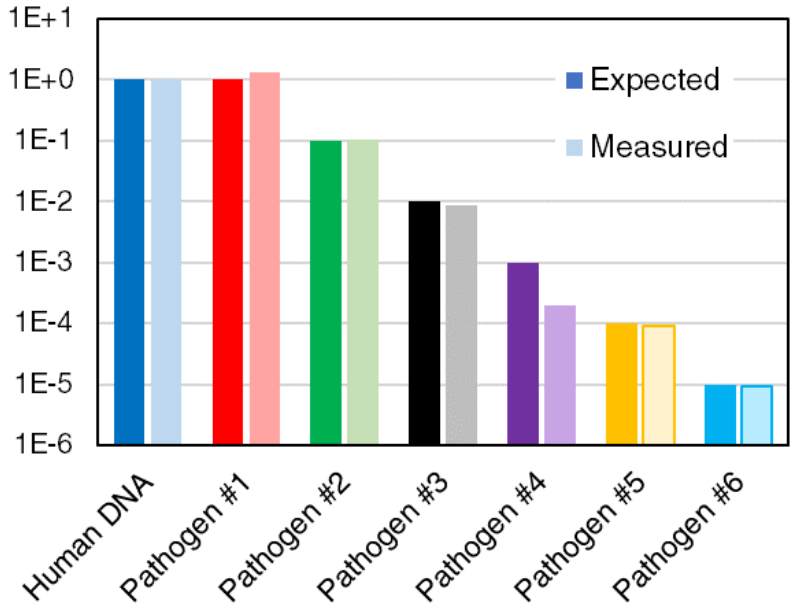
Source	Abundance*
Human DNA	10^{1}
Pathogen #1	10^{-1}
Pathogen #2	10^{-2}
Pathogen #3	10^{-3}
Pathogen #4	10^{-4}
Pathogen #5	10^{-5}
Pathogen #6	10^{-6}

Pool



Abundance* is genome copy number relative to human reference DNA

We might not be able to count cells accurately, but we can count DNA molecules ***very*** accurately



Sample Preparation

Metagenomic Analysis

Develop Microbial Metagenomic Reference Materials

- Description
  - 19+1 Bacteria+Human
- Features
  - Near neighbors
  - High/Low GC content
  - Gram +/-
  - Genome sizes
  - AMR genes
  - Disease sites

Number	ATCC	Organism	Genome Assembly	Genome size	G+C	Conc (ng/uL)	nmol/uL
MG-001	ATCC 43895	*Escherichia coli o147:h7*	IHQ Draft	5389465	50.5	98	1.81E-05
MG-002	ATCC BAA 2309	*Escherichia coli o104:h4*	IHQ Draft	6746060	50.7	92	1.36E-05
MG-003	ATCC 700720	*Salmonella enterica enterica*	IHQ Draft	7714010	52.2	135	1.74E-05
MG-004	ATCC 12324	*Salmonella enterica arizonae*	IHQ Draft	5297117	51.4	167	3.15E-05
MG-005	ATCC BAA 44	*Staphyloccus aureus*	IHQ Draft	3067805	32.9	124	4.03E-05
MG-006	ATCC 12600	*Staphyloccus aureus*	IHQ Draft	2967254	32.9	98	3.30E-05
MG-007	ATCC 12228	*Staphyloccus epidermidis*	Draft	2562881	32	113	4.42E-05
MG-008	ATCC BAA 47	*Pseudomonas aeruginosa*	IHQ Draft	7880267	66.5	153	1.94E-05
MG-009	ATCC 19606	*Acinetobacter baumannii*	Draft	3962920	40	128	3.23E-05
MG-010	ATCC 13077	*Neisseria meningitidis*	Draft	2203117	51	98	4.45E-05
MG-013	ATCC 12344	*Streptococcus pyogenes*	IHQ Draft	3957052	38.5	96	2.43E-05
MG-014	ATCC 19433	*Enterococcus faecalis*	IHQ Draft	2885194	37.6	81	2.80E-05
MG-016	ATCC 27061	*Achromobacter xylosoxidans*	Draft	6792745	66	133	1.96E-05
MG-017	ATCC 35654	*Aeromonas hydrophila*	Draft	5531020	54	93	1.67E-05
MG-018	ATCC 13883	*Klebsiella pneumoniae*	IHQ Draft	6010037	57.4	105	1.75E-05
MG-019	ATCC 25931	*Shigella sonnei*	IHQ Draft	4980291	51	109	2.20E-05
MG-021	ATCC 35016	*Vibrio furnissii*	IHQ Draft	5043863	50.8	95	1.88E-05
MG-022	ATCC 19115	*Listeria monocytogenes*	IHQ Draft	2977009	38	86	2.90E-05
MG-024	ATCC 33152	*Legionella pneumophila*	IHQ Draft	2977010	38.3	109	3.66E-05
HG-001		*Homo sapiens sapiens*			42.0		

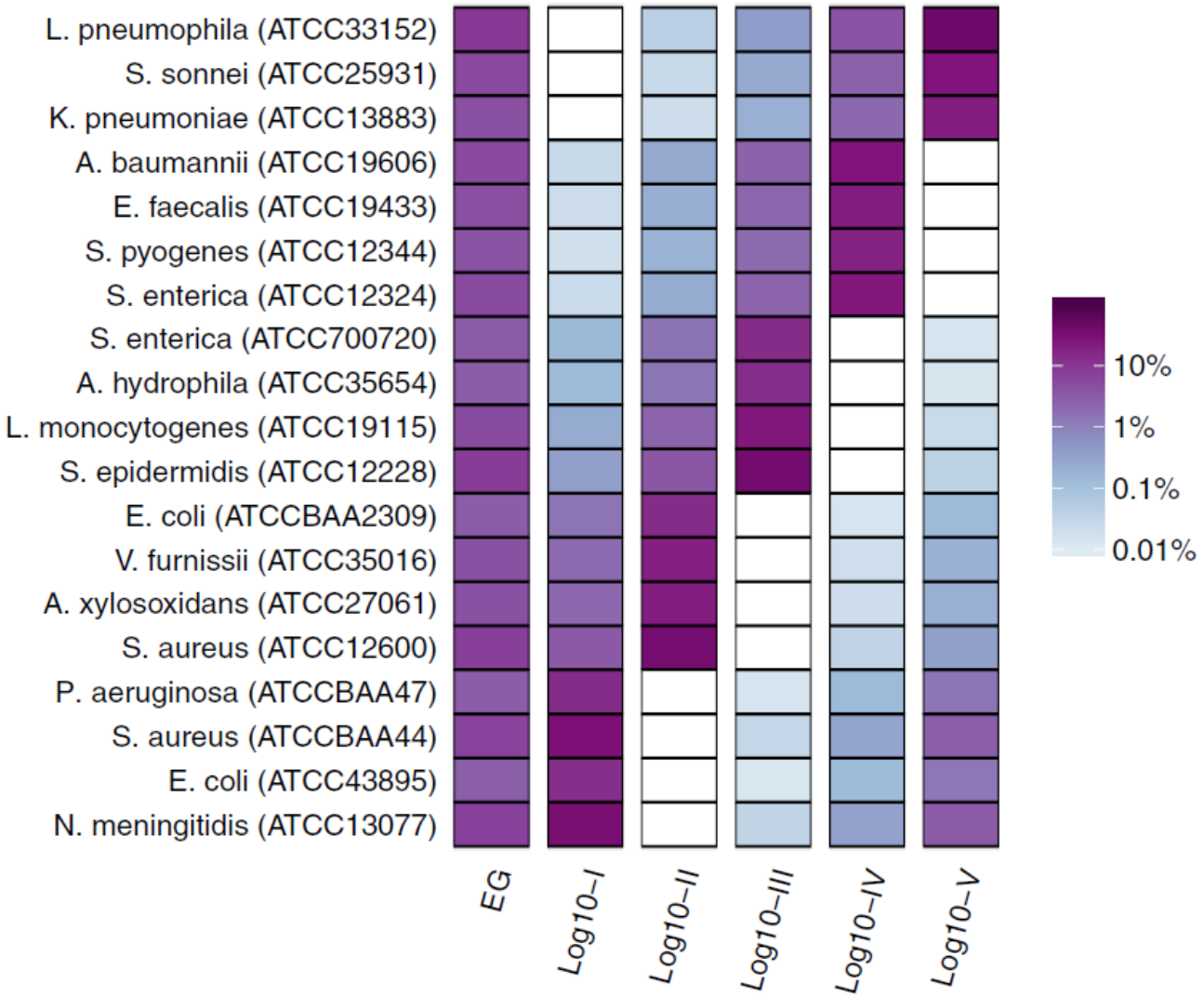
RM Characterization

Each tube will contain a single genome and will be characterized for the following metrics:

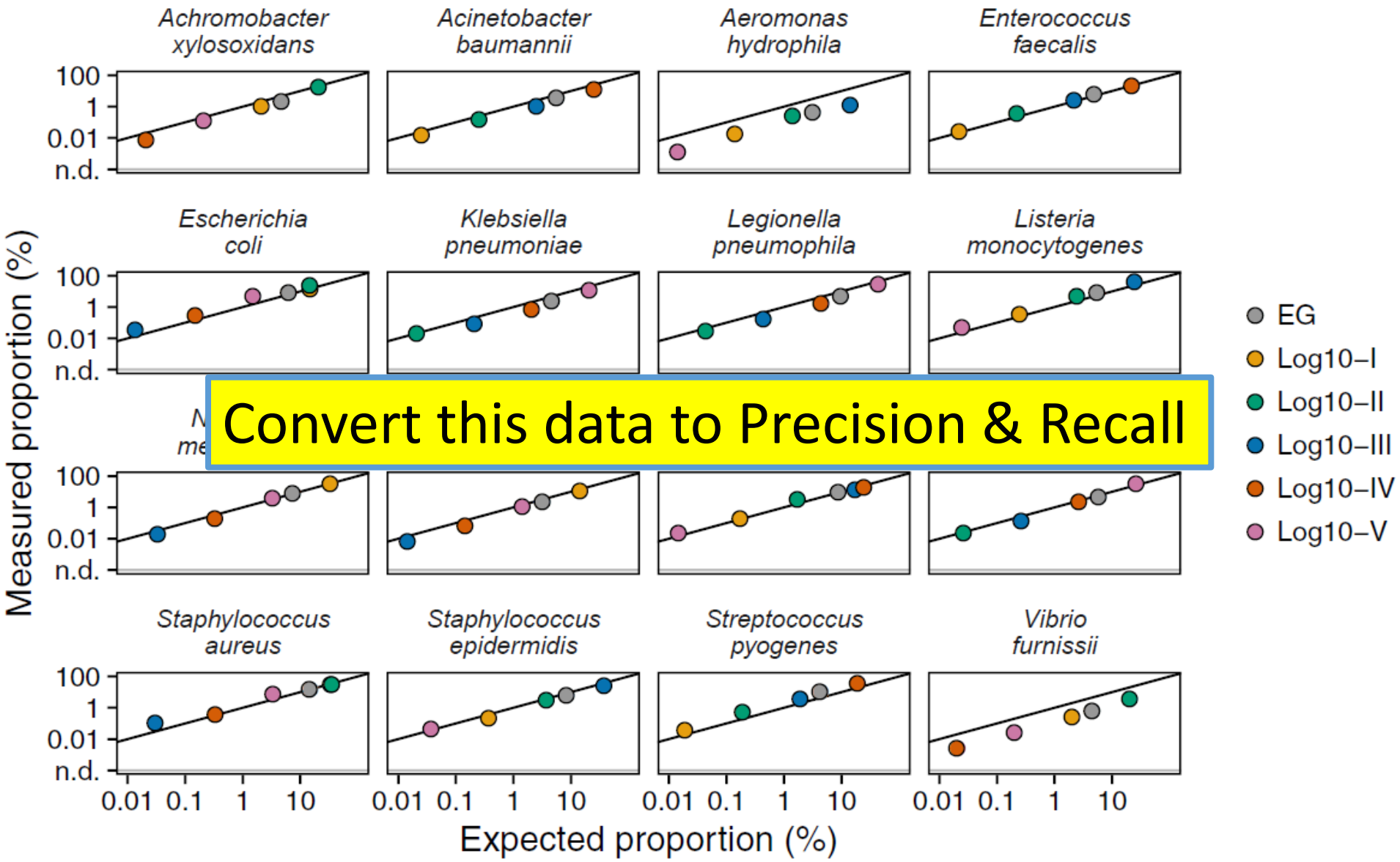
Tube Rack – 20 Tubes

- Genome Assembly – Long Read Sequencing
- Genomic Contaminants
  - Environmental/Reagent/Platform Contaminants
- Quantity and Homogeneity
  - dPCR
  - UV_{260} Absorption
  - Fluorescence – dsDNA – “Qubit”
- DNA Stability
  - ddPCR up to 6 months

Making Model Mixtures (Latin Square-like)



Results by species – Experimental + `Centrifuge`



Convert this data to Precision & Recall

Jason Kralj and

Dieter Tourlousse

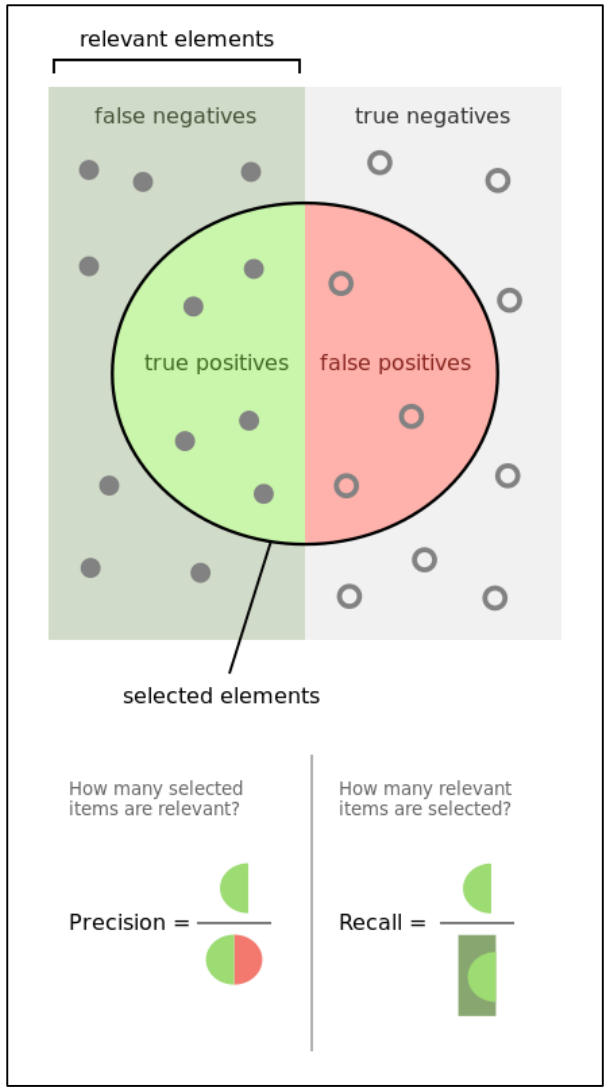
Relative Performance Metrics

$$Sensitivity\ (TPR) \equiv \frac{TP}{TP + FN}$$

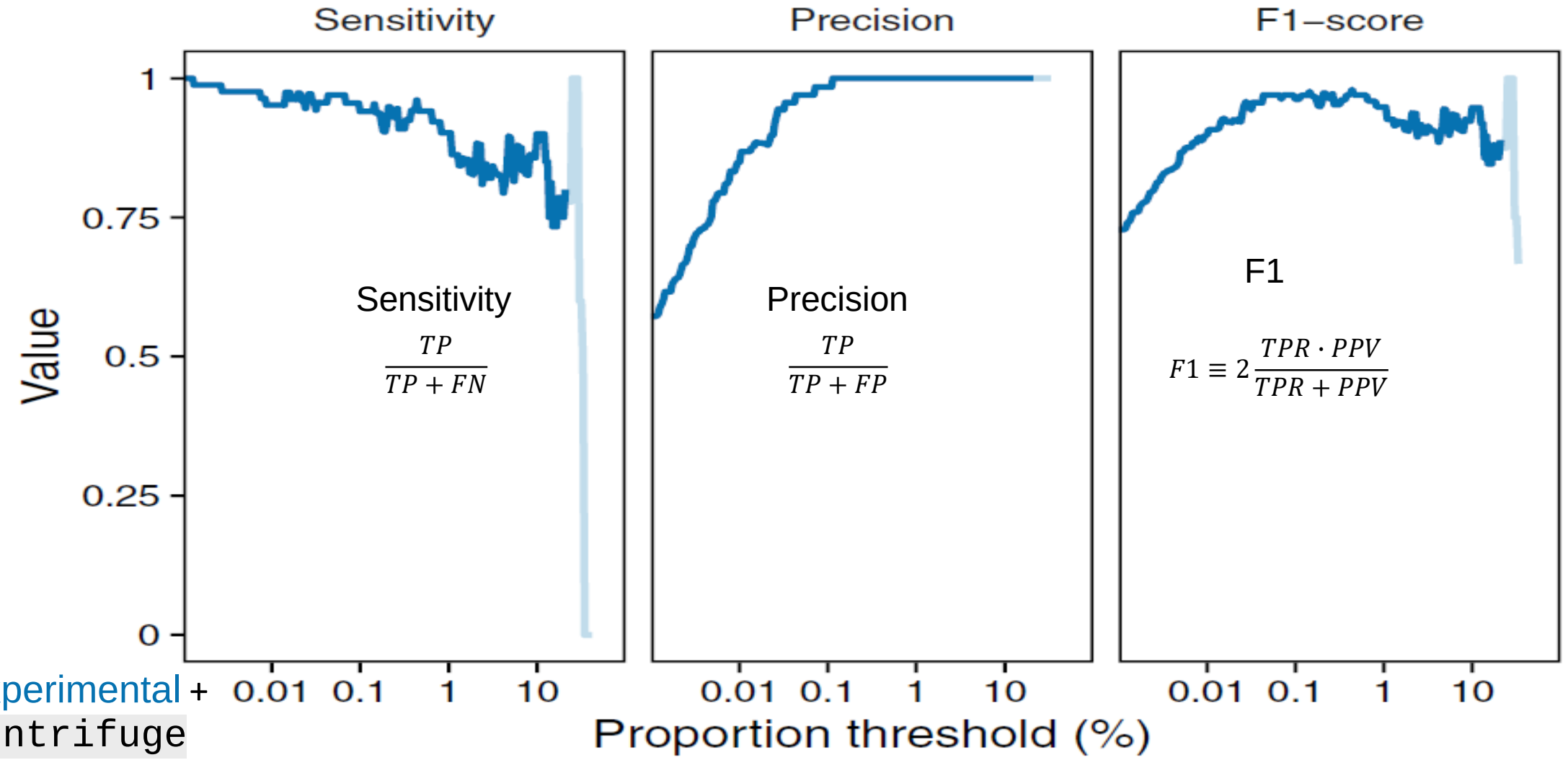
$$Precision\ (PPV) \equiv \frac{TP}{TP + FP} = 1 - FDR$$

$$F1 \equiv 2\frac{TPR \cdot PPV}{TPR + PPV}$$

(Harmonic mean of TPR & PPV)

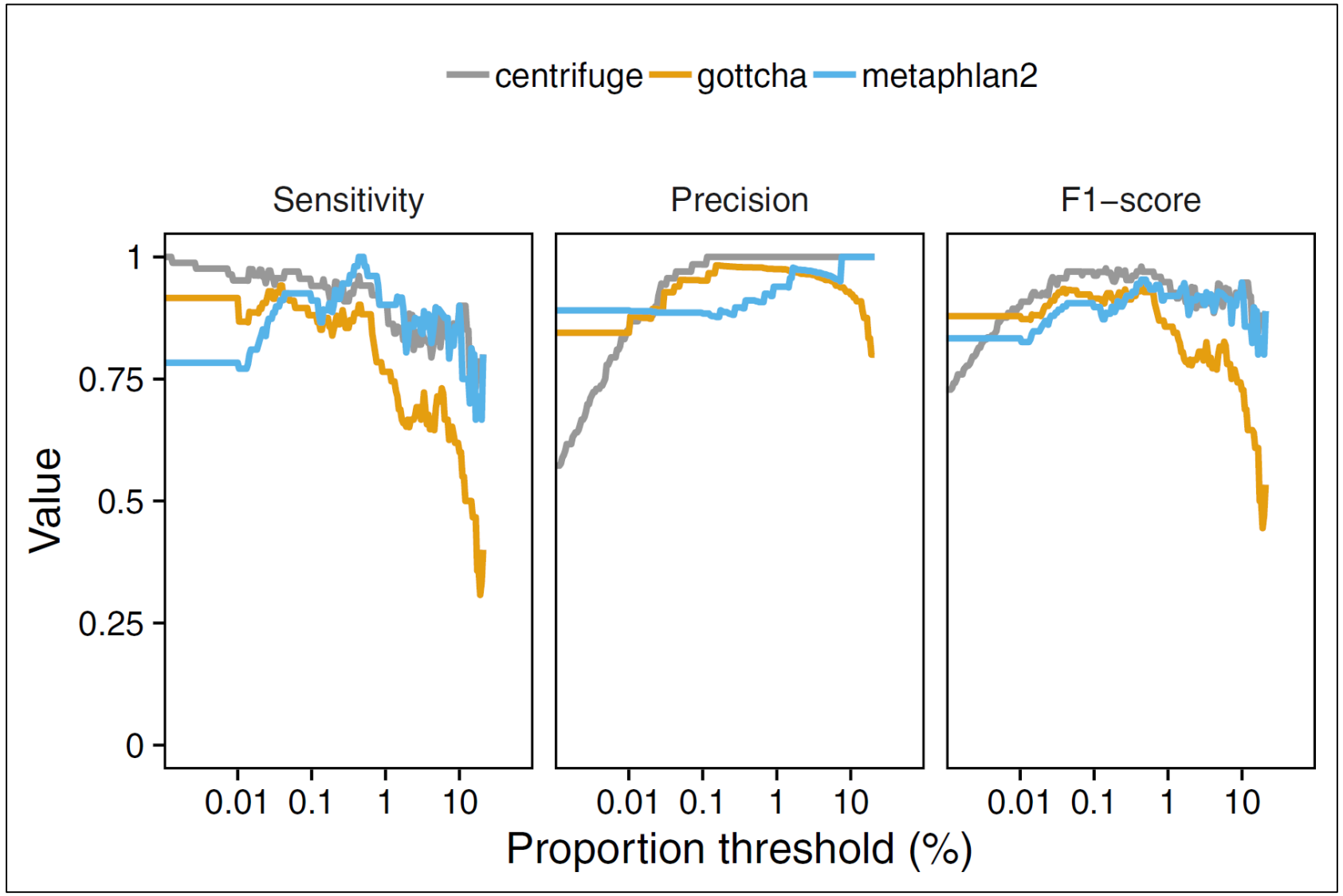


Performance Metrics Summary



Experimental + `Centrifuge`

Effect of DNA Taxonomic Classifiers on Performance



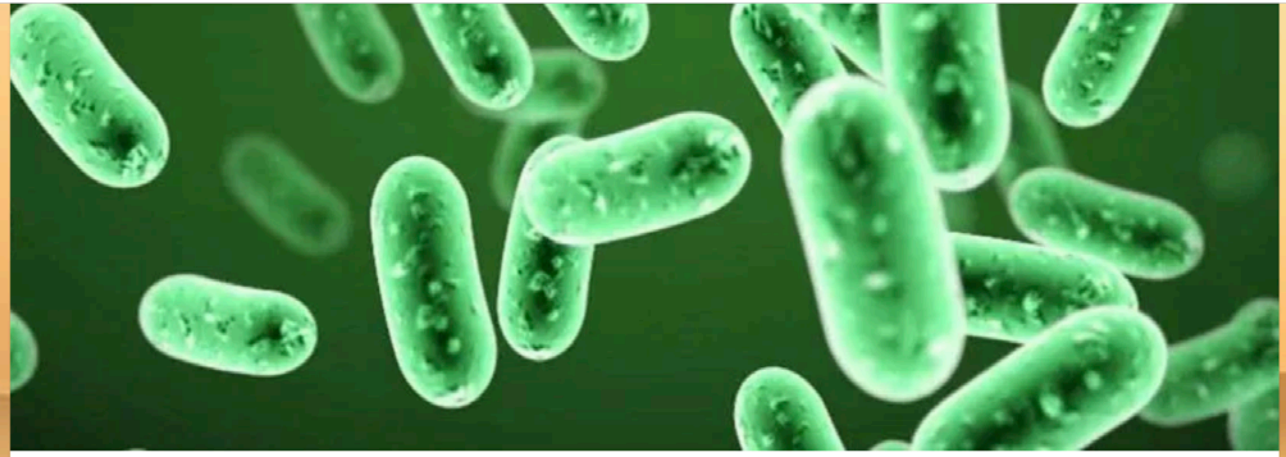
Experimental

>97 Taxonomic Profiling Tools Exist (more like ~110)

https://microbe.land/2018/12/13/97-metagenomics-classifiers/

It's the small stuff that matters…

Search …



97 Metagenomics Classifiers…

And growing…

Below is a simple bibliography of metagenomics classification algorithms, built from the GoogleDoc I created some time ago (2015?) and now maintained over at Zotero. So far, I've identified 97 (!!!) papers that all are trying to solve the same problem: ***what is in this sample?***

It's pretty incredible – I wonder at how many newly minted PhDs are represented in this list. If I put a more skeptical hat on, I also wonder whether the community is chasing an classification-prediction asymptote, and whether we are well past the point of

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Profiling the Profilers

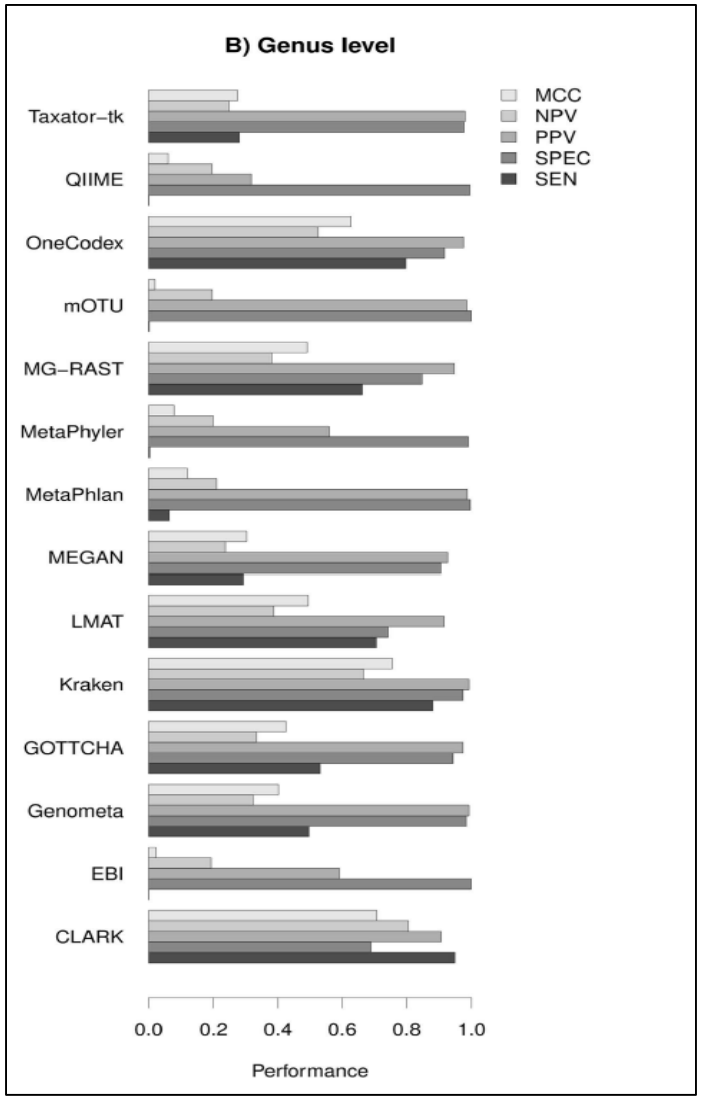
An evaluation of the accuracy and speed of metagenome analysis tools

Stinus Lindgreen[1,2,3,†], Karen L. Adair[1,2] & Paul P. Gardner[1,2]

SCIENTIFIC REPORTS | 6:19233 | DOI: 10.1038/srep19233

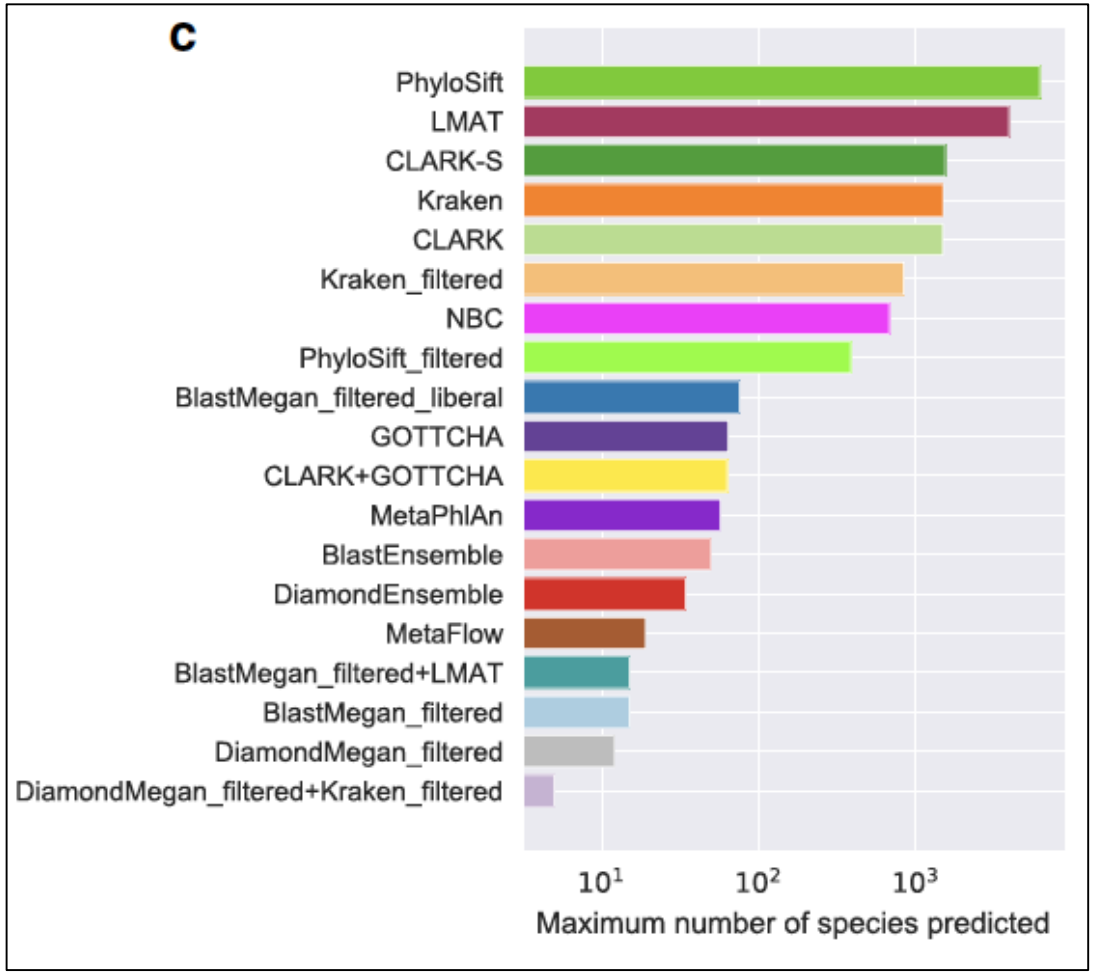
Method	TP	FP	TN	FN	SEN	SPEC	PPV	NPV	MCC
CLARK	23571770	1170750	4718015	0	1.0000	0.8012	0.9527	1.0000	0.8736
EBI	13879	9939	5782564	23654153	0.0006	0.9983	0.5826	0.1964	−0.0157
Genometa	11732372	99524	5782564	11846075	0.4968	0.9831	0.9917	0.3280	0.3926
GOTTCHA	12756512	0	5782564	10921460	0.5388	1.0000	1.0000	0.3462	0.4327
Kraken	21305328	86	5782545	2372576	0.8998	1.0000	1.0000	0.7091	0.7991
LMAT	15166868	1592274	4295866	8405528	0.6433	0.7296	0.9050	0.3382	0.3023
MEGAN	12868515	63500	5782564	10745957	0.5452	0.9891	0.9951	0.3499	0.4305
MetaPhlan	1507348	0	5782564	22170624	0.0636	1.0000	1.0000	0.2069	0.1150
MetaPhyler	133836	713	5781915	23544072	0.0057	0.9999	0.9947	0.1972	0.0327
MG-RAST	16554882	44309	5782562	7078782	0.7015	0.9924	0.9973	0.4496	0.5605
mOTU	47846	0	5782564	23630126	0.0020	1.0000	1.0000	0.1966	0.0200
OneCodex	21808925	320	5782541	1868749	0.9210	0.9999	1.0000	0.7558	0.8345
QIIME	12914	37	5782564	23665021	0.0005	1.0000	0.9972	0.1964	0.0102
Taxator-tk	11610500	1898276	5782562	10169197	0.5335	0.7537	0.8593	0.3625	0.2537

Table 2. Phylum level performance metrics for the individual methods. Average numbers for the simulated data sets are given. The metrics are true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) as well as sensitivity (SEN), specificity (SPEC), positive predictive value (PPV), negative predictive value (NPV) and Matthew's Correlation Coefficient (MCC).



Tools typically trade-off strengths and weaknesses

Profiling the Profilers



RESEARCH Open Access

Comprehensive benchmarking and ensemble approaches for metagenomic classifiers

Alexa B. R. McIntyre[1,2,3], Rachid Ounit[4], Ebrahim Afshinnekoo[2,3,5], Robert J. Prill[6], Elizabeth Hénaff[2,3], Noah Alexander[2,3], Samuel S. Minot[7], David Danko[1,2,3], Jonathan Foox[2,3], Sofia Ahsanuddin[2,3], Scott Tighe[8], Nur A. Hasan[9,10], Poorani Subramanian[9], Kelly Moffat[9], Shawn Levy[11], Stefano Lonardi[4], Nick Greenfield[7], Rita R. Colwell[9,12], Gail L. Rosen[13*] and Christopher E. Mason[2,3,14*]

Credit:
Alexa McIntyre

Issues with Reference Genome Databases

- Metagenomic Analyses Requires a Reference Database of Known Genomic Sequences (e.g. Genbank)

- We can only “see” what is in our databases

- So, how representative are the reference databases?

Reference Database Representation =
Number of Species in Database/Number of Species on Earth

Issues with Reference Genome Databases

- Currently, we have genome sequence data for ~38,000 different species in NCBI (~27,000 microbial species)
- So, how representative is this reference database?
- Need to know how many different species exist on earth…
- Any guesses?

Issues with Reference Genome Databases

- A recent estimate of the number of s
  - $1x10^{12}$

Currently, we have genome sequence data for ~38,000 different species in NCBI (~27,000 microbial species)

So our current databases represent 0.0001% of all species on Earth

The New York Times

TAKE A NUMBER

Earth May Be Home to a Trillion Species of Microbes

A scanning electron micrograph of fecal microbes. Estimates of the number of microbial species continue to grow. David Scharf/ Science Source

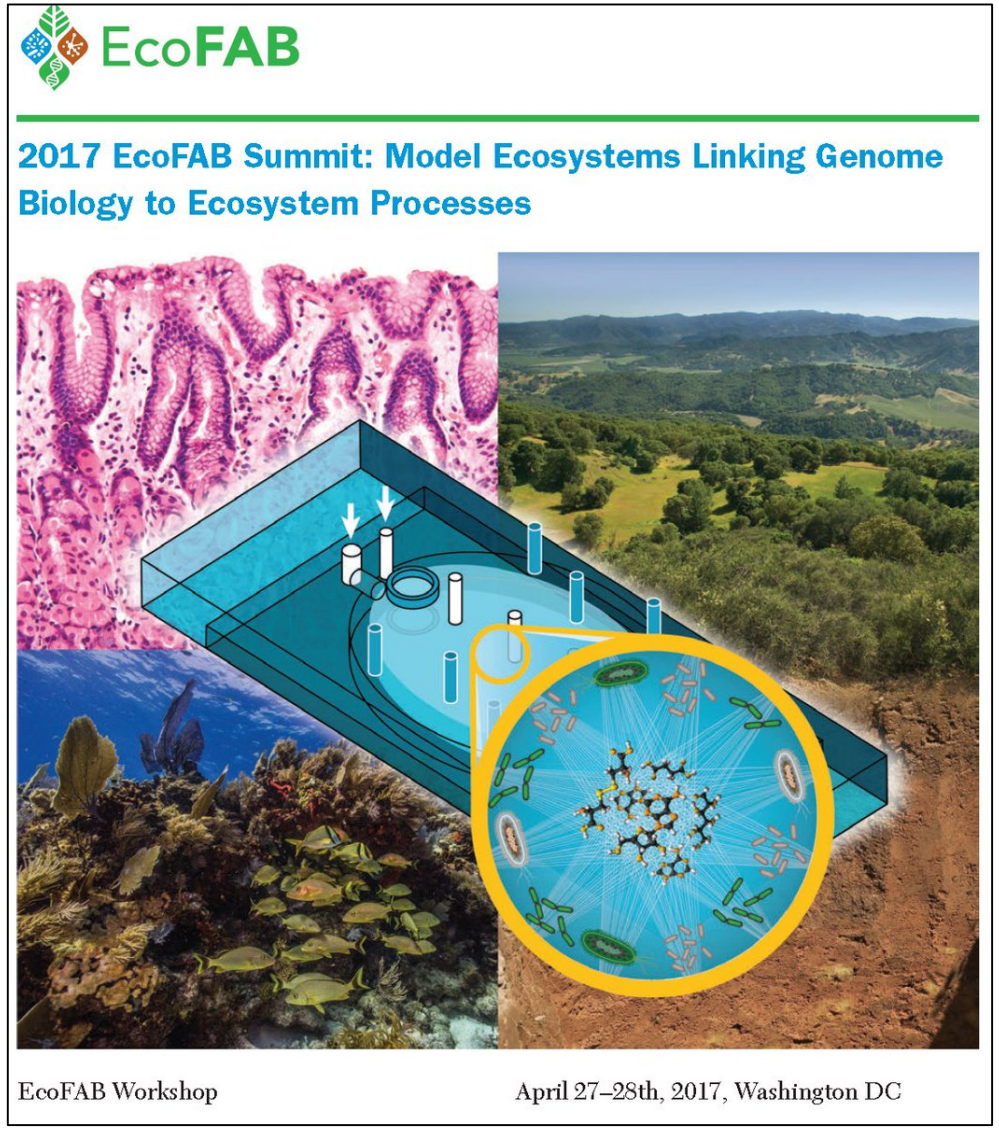
By Nicholas Bakalar

May 23, 2016

According to a new estimate, there are about one trillion species of microbes on Earth, and 99.999 percent of them have yet to be discovered.

As recently as 1998, the number of microbial species was thought

Fabricated Microbial Ecosystems



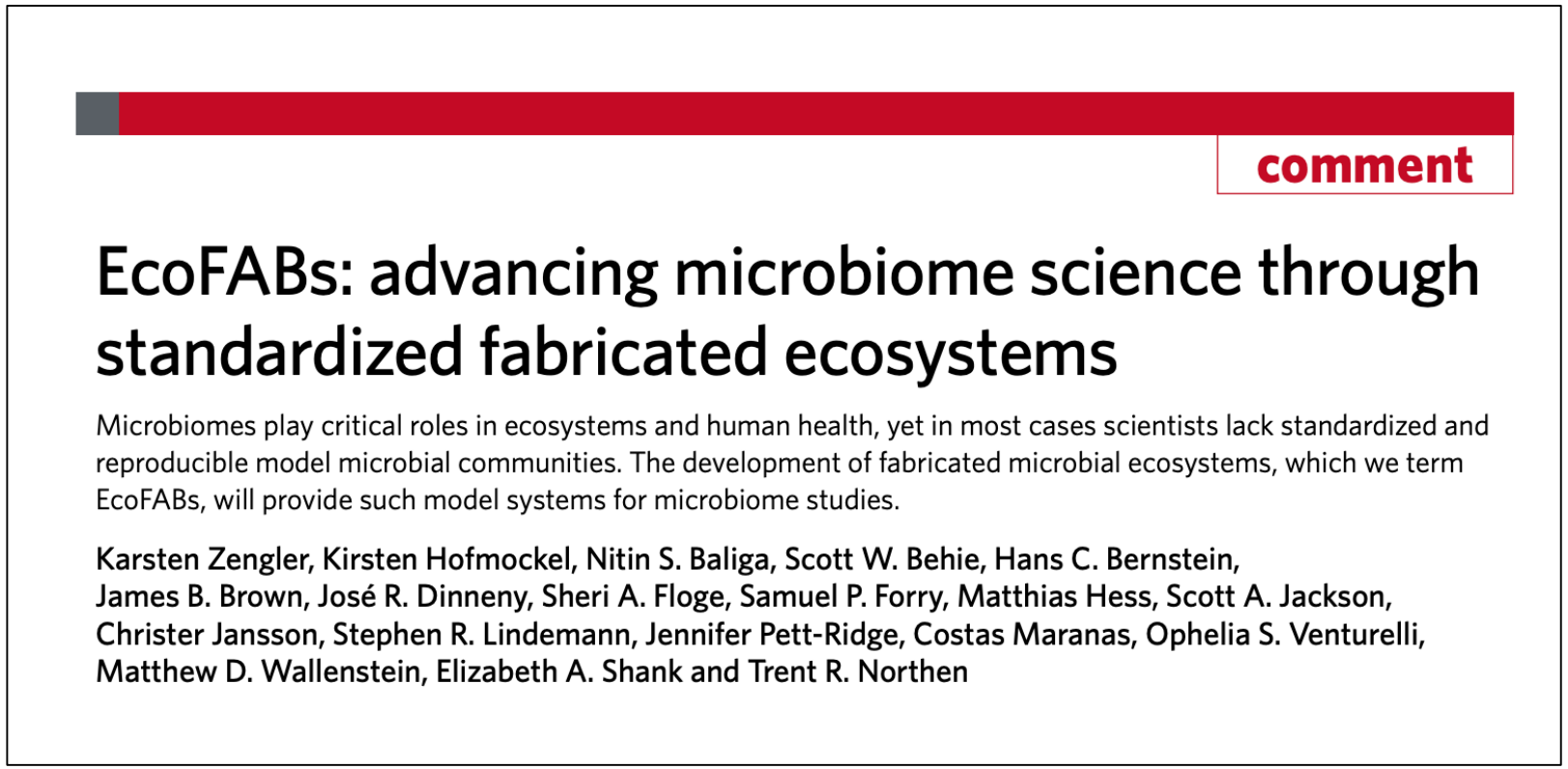
Problem:

- No two microbiome samples are the same. How do we reproduce results within our lab and across lab?
- Need a microbiome "model system" to allow reproducible, systematic studies across different laboratories

Solution:

- Develop reproducible fabricated ecosystems. Devices for standardized and reproducible analysis of both synthetic consortia and natural microbiomes in simulated and natural environments under controlled conditions.
- EcoFab – A Consortia – Berkeley National Lab

Fabricated Microbial Ecosystems



comment

EcoFABs: advancing microbiome science through standardized fabricated ecosystems

Microbiomes play critical roles in ecosystems and human health, yet in most cases scientists lack standardized and reproducible model microbial communities. The development of fabricated microbial ecosystems, which we term EcoFABs, will provide such model systems for microbiome studies.

Karsten Zengler, Kirsten Hofmockel, Nitin S. Baliga, Scott W. Behie, Hans C. Bernstein, James B. Brown, José R. Dinneny, Sheri A. Floge, Samuel P. Forry, Matthias Hess, Scott A. Jackson, Christer Jansson, Stephen R. Lindemann, Jennifer Pett-Ridge, Costas Maranas, Ophelia S. Venturelli, Matthew D. Wallenstein, Elizabeth A. Shank and Trent R. Northen

Nature Methods | VOL 16 | JULY 2019 | 567–571 |
www.nature.com/naturemethods

An important founding principle:

EcoFabs should be open-source and amenable to “typical” research laboratory environments