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CRISPR Diagnostics for Tackling Antimicrobial Resistance

Dr. Nikki Weckman

UNIVERSITY OF TORONTO
FACULTY OF APPLIED SCIENCE & ENGINEERING
Centre for Global Engineering

Nicole.Weckman@utoronto.ca
weckmanlab.com

Disclosures

- I am a co-founder, shareholder and the Chief Technology Officer at 52 North Health

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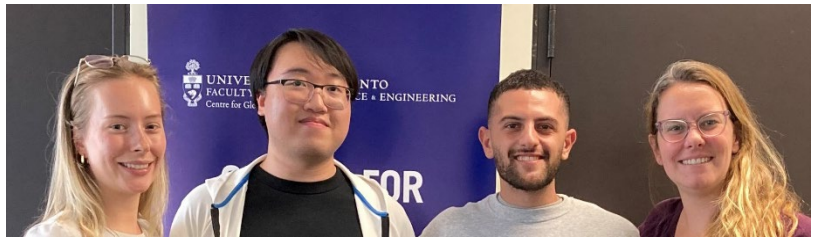
With thanks for funding, time, and expertise:



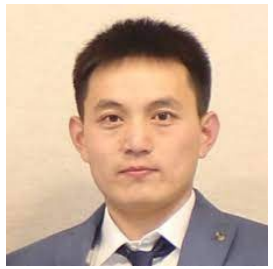
UNIVERSITY OF TORONTO

EPIC Emerging & Pandemic Infections Consortium

UNIVERSITY OF TORONTO
FACULTY OF APPLIED SCIENCE & ENGINEERING
Centre for Global Engineering

NSERC CRSNG

Keyser Lab

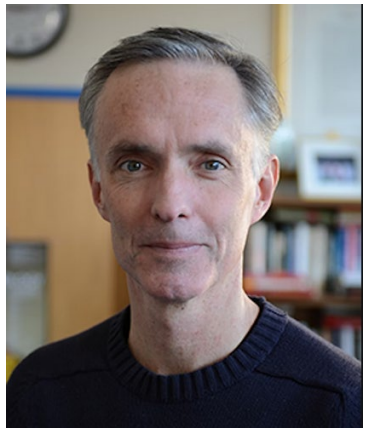


Oxford NANOPORE Technologies

OPdIA Office of Postdoctoral Affairs

CANADA-UK FOUNDATION

WYSS INSTITUTE for Biologically Inspired Engineering



Wadsworth Center NYSDOH

Collins Lab

By 2050 Antimicrobial Resistance could have:

- Caused up to **10 million deaths per year**
- Decreased productivity costing

  US$100 trillion

O'Neill, J. "Antimicrobial resistance." Tackling a crisis for the health and wealth of nations (2014).

Diagnostics are critical for tackling antimicrobial resistance

Increase awareness and surveillance

Infection prevention and control

Reduce exposure to non-health antibiotics

Antibiotic stewardship
Requires surveillance, access, and diagnostics

Invest in vaccinations, new therapeutics, diagnostics

47% of the global population has little to no access to diagnostics

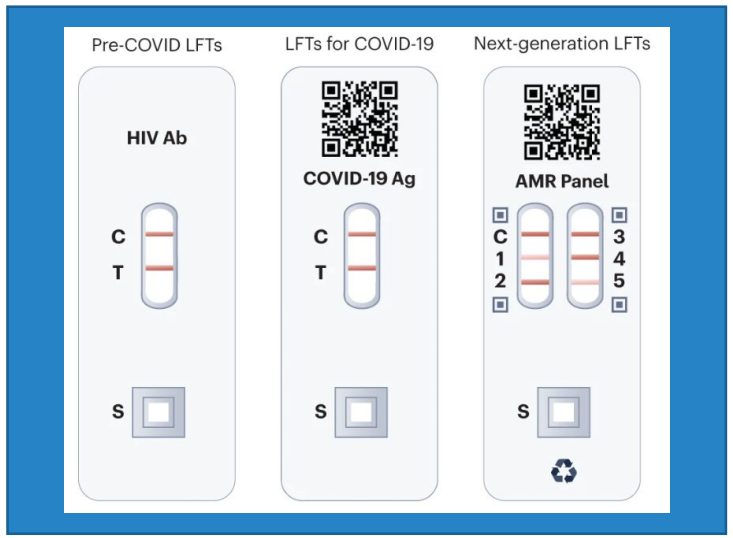
Fleming, Kenneth A., et al. "The Lancet Commission on diagnostics: Transforming access to diagnostics." The Lancet 398.10315 (2021): 1997-2050.

Photo Credit Kenn Chaplin

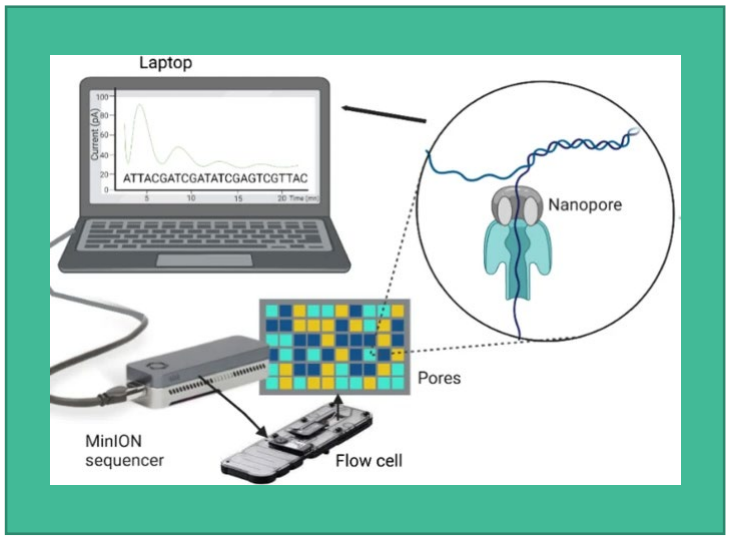
We wish to acknowledge this land on which the University of Toronto operates. For thousands of years it has been the traditional land of the Huron-Wendat, the Seneca, and the Mississaugas of the Credit. Today, this meeting place is still the home to many Indigenous people from across Turtle Island and we are grateful to have the opportunity to work on this land.

Diverse sensor technologies are used in global healthcare

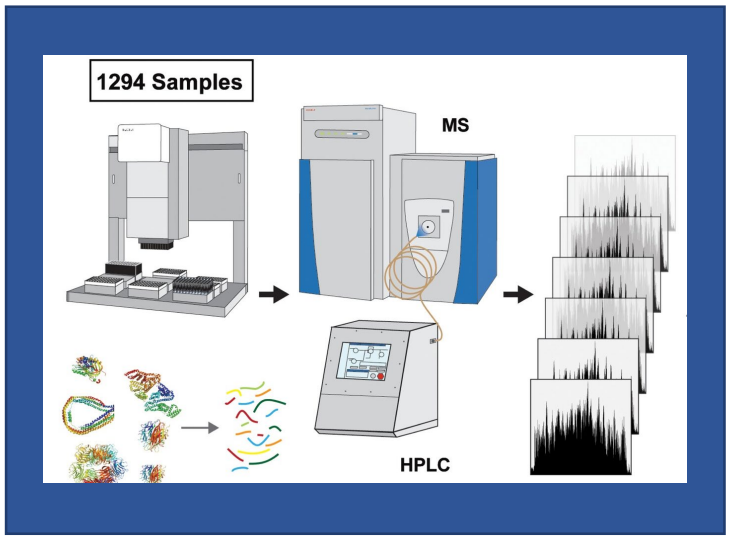
Decentralized & low resource settings



Emerging technologies for multi-use settings



Well-equipped centralized laboratories

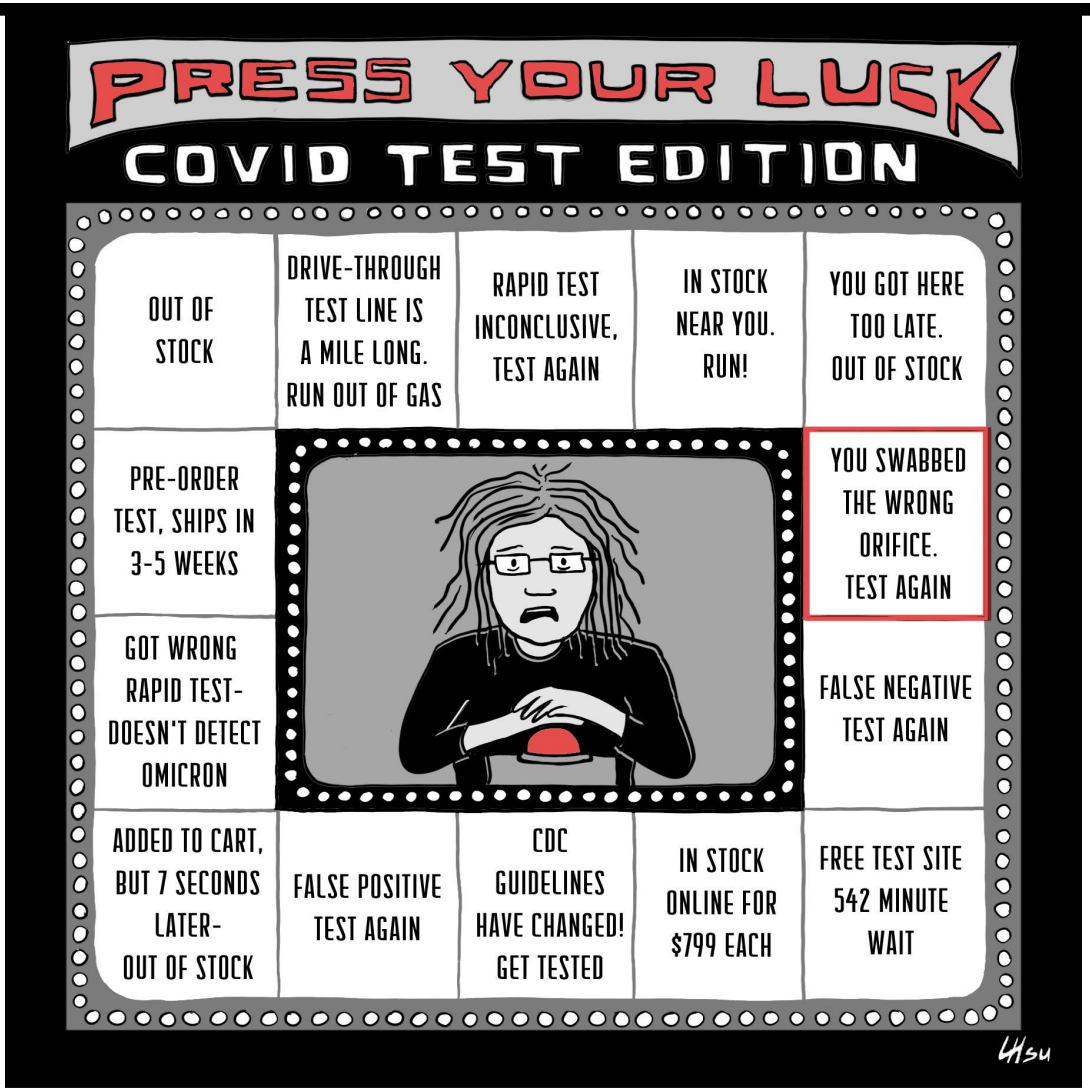


Budd, J., Miller, B.S., **Weckman, N.E.** et al. Lateral flow test engineering and lessons learned from COVID-19. Nat Rev Bioeng 1, 13–31 (2023).

Wasswa, F.B., et al. MinION Whole-Genome Sequencing in Resource-Limited Settings: Challenges and Opportunities. Curr Clin Micro Rpt 9, 52–59 (2022).

Geyer, P.E., et al. "Proteomics reveals the effects of sustained weight loss on the human plasma proteome." Molecular systems biology 12.12 (2016): 901.

New diagnostics: what are the ideal characteristics?



CartoonStock.com

- REASSURED
  - Real-time connectivity
  - Ease of specimen collection
  - Affordable
  - Sensitive
  - Specific
  - User-friendly
  - Rapid and robust
  - Equipment free or simple
  - Environmentally friendly
  - Deliverable to users

Focus: Sensitive, Specific

Inter-related: Real-time connectivity, Ease of specimen collection, Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment free or simple, Environmentally friendly, Deliverable to users

- **Quantitative and Multiplexed**

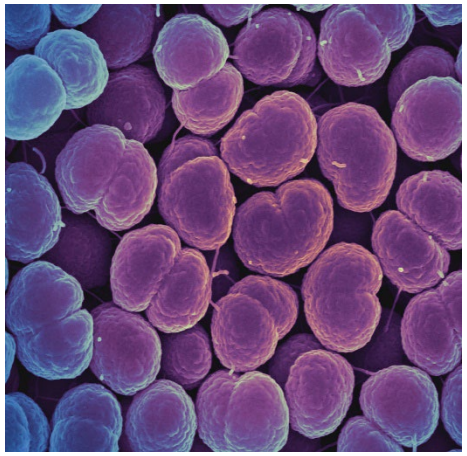
Land, Kevin J., et al. "REASSURED diagnostics to inform disease control strategies, strengthen health systems and improve patient outcomes." *Nature microbiology* 4.1 (2019): 46-54.

Synthetic biology for sample to answer bioanalysis

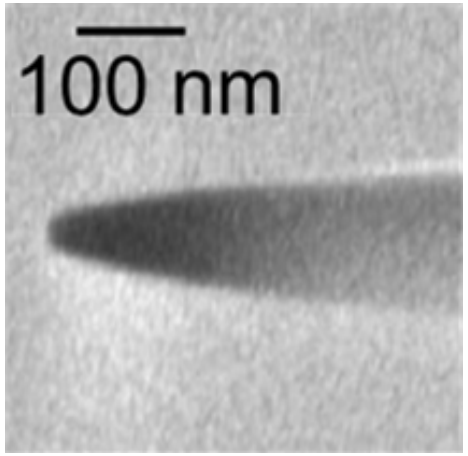
Multiplexed and quantitative micro & nanoscale transducers

Commercial & User Centered Design

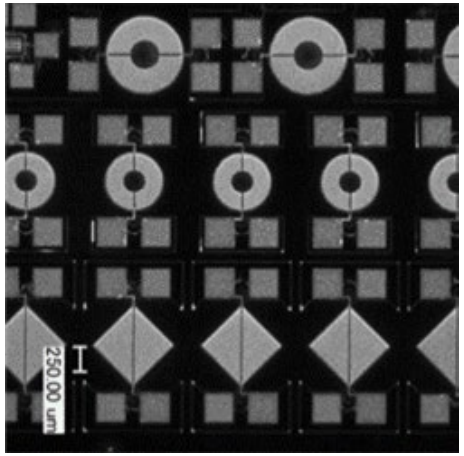
Antifungal Resistance:
Candida Auris



STI Resistance:
N. gonorrhoea



Nanopores



MEMS resonators

POC testing

Photo Credit CDC, NIH

Synthetic biology for sample to answer bioanalysis

Antifungal Resistance:
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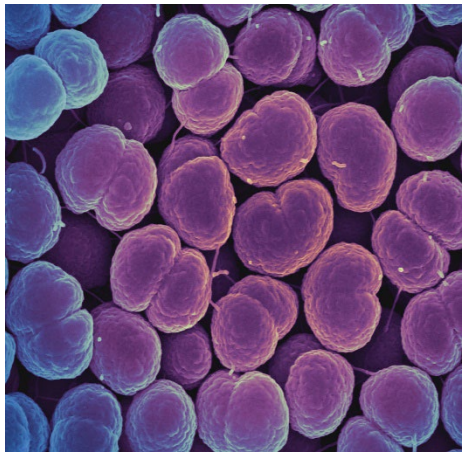
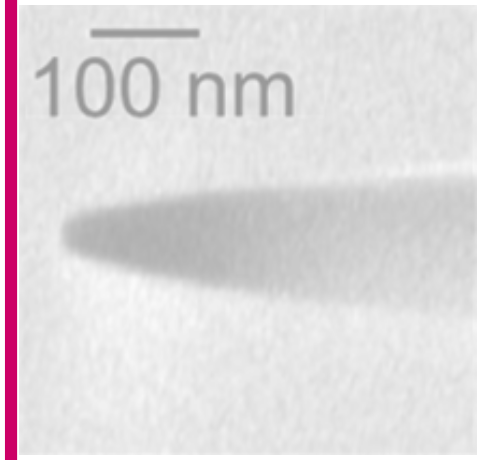
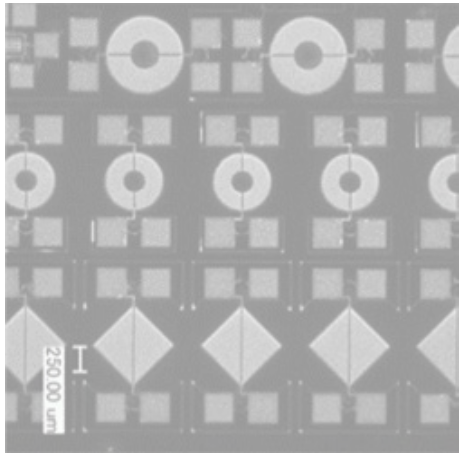


STI Resistance:
N. gonorrhoea

Multiplexed and quantitative micro & nanoscale transducers



Nanopores



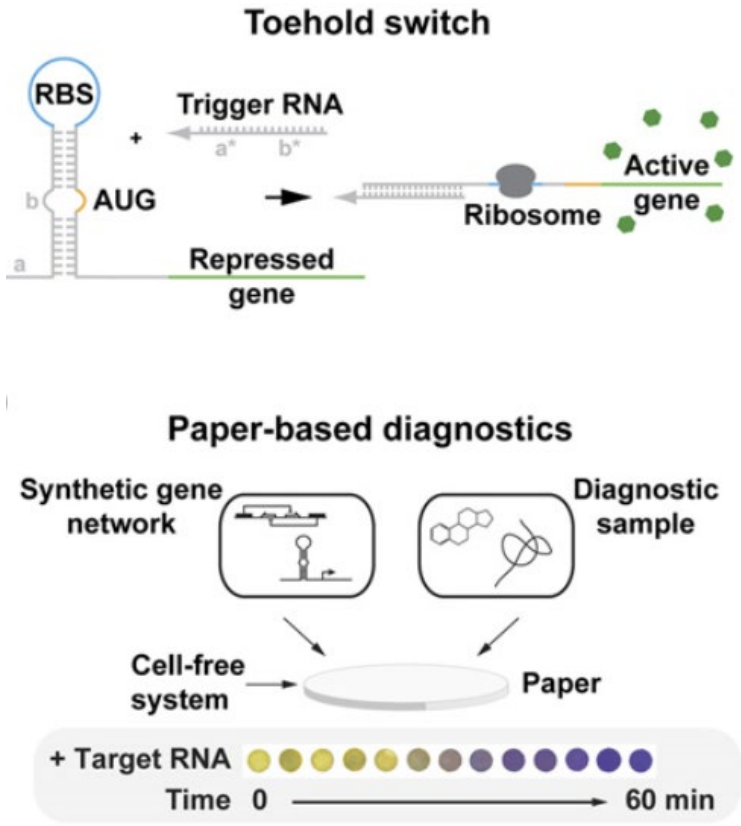
MEMS resonators

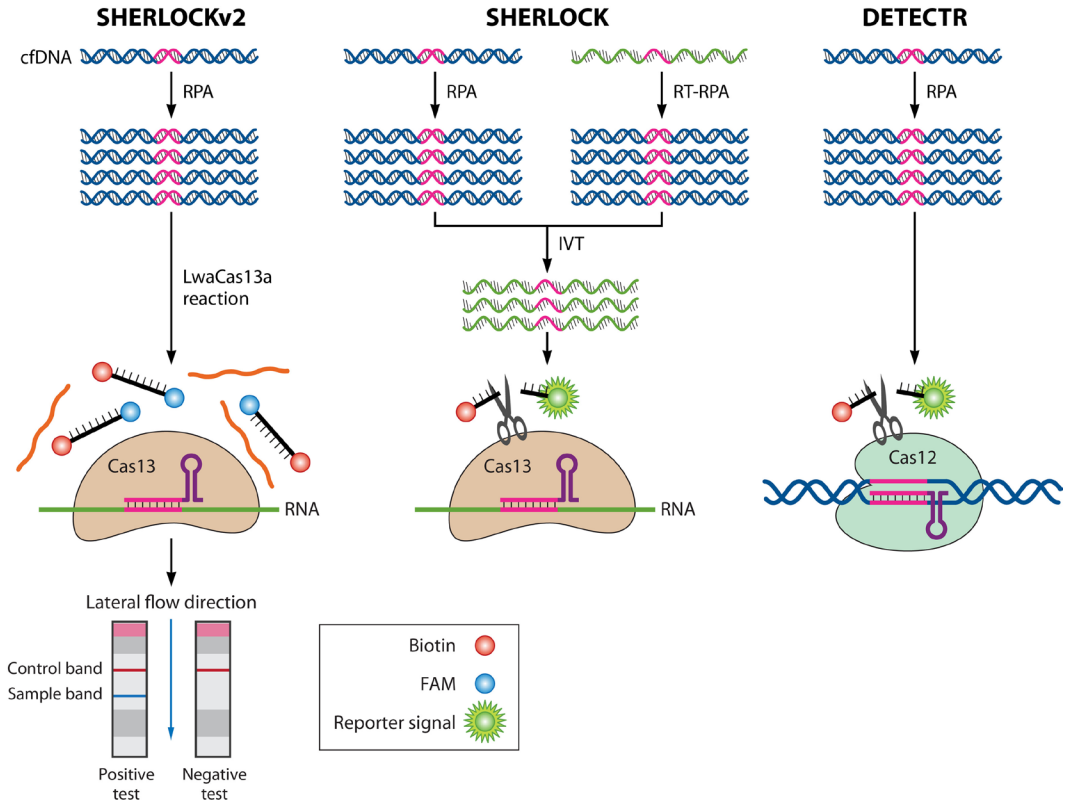
Commercial & User Centered Design

POC testing

Photo Credit CDC, NIH

Synthetic biology for diagnostics



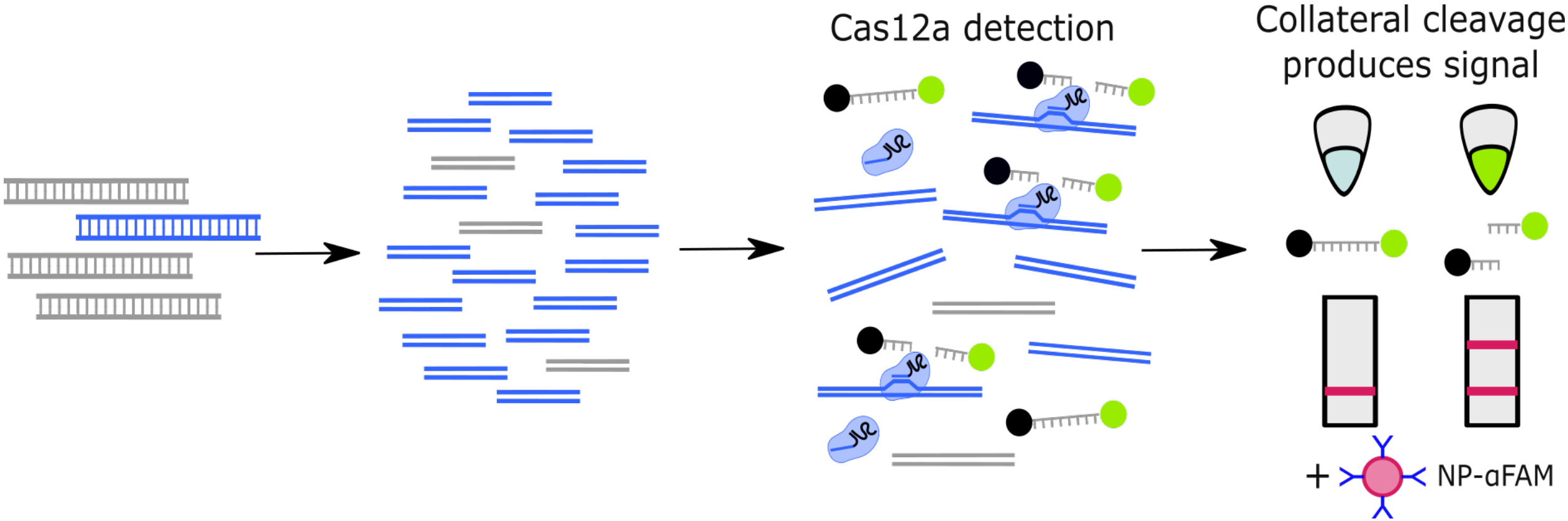


Slomovic, Shimyn, Keith Pardee, and James J. Collins. "Synthetic biology devices for in vitro and in vivo diagnostics." *Proceedings of the National Academy of Sciences* 112.47 (2015): 14429-14435.

Further reading:
-Gootenberg et al. *Science.* 356.6336 (2017):438-442. doi: 10.1126/science.aam9321
-Chen et al. *Science.* 360.6387(2018):436-439. doi: 10.1126/science.aar6245

M.I.Mustafa, A.M. Makhawi. "SHERLOCK and DETECTR: CRISPR-Cas systems as potential rapid diagnostic tools for emerging infectious diseases." *Journal of Clinical Microbiology* 59.3 (2021): 10-1128.

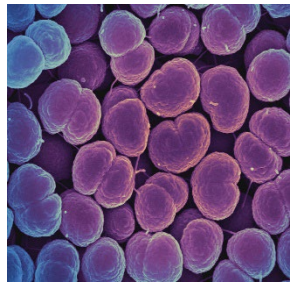
SHERLOCK Assay for Nucleic Acid Detection



Isothermal amplification improves sensitivity but limits quantification

Antifungal Resistance:
Candida Auris

- Expanding detection of *Candida* species
- Rapidly screening for antifungal susceptibility
- Testing from samples (PHO)



STI Infections:
MDR *N. gonorrhoea*

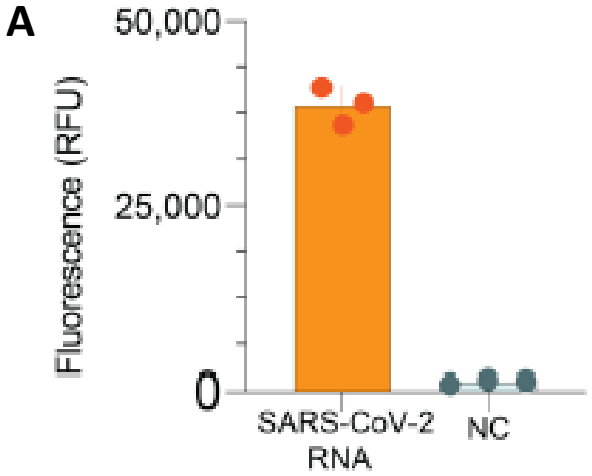
- Rapid diagnostic to meet WHO and FIND TPP for STI screening
- Community engagement via Young African Refugees for Integral Development (YARID), Kampala, Uganda

Dr. Rob Kozak
Sunnybrook Research Institute
(EPIC, U of Toronto)

Prof Carmen Logie
CRC in Global Health Equity and Social Justice with Marginalized Populations

Photo Credit CDC, NIH

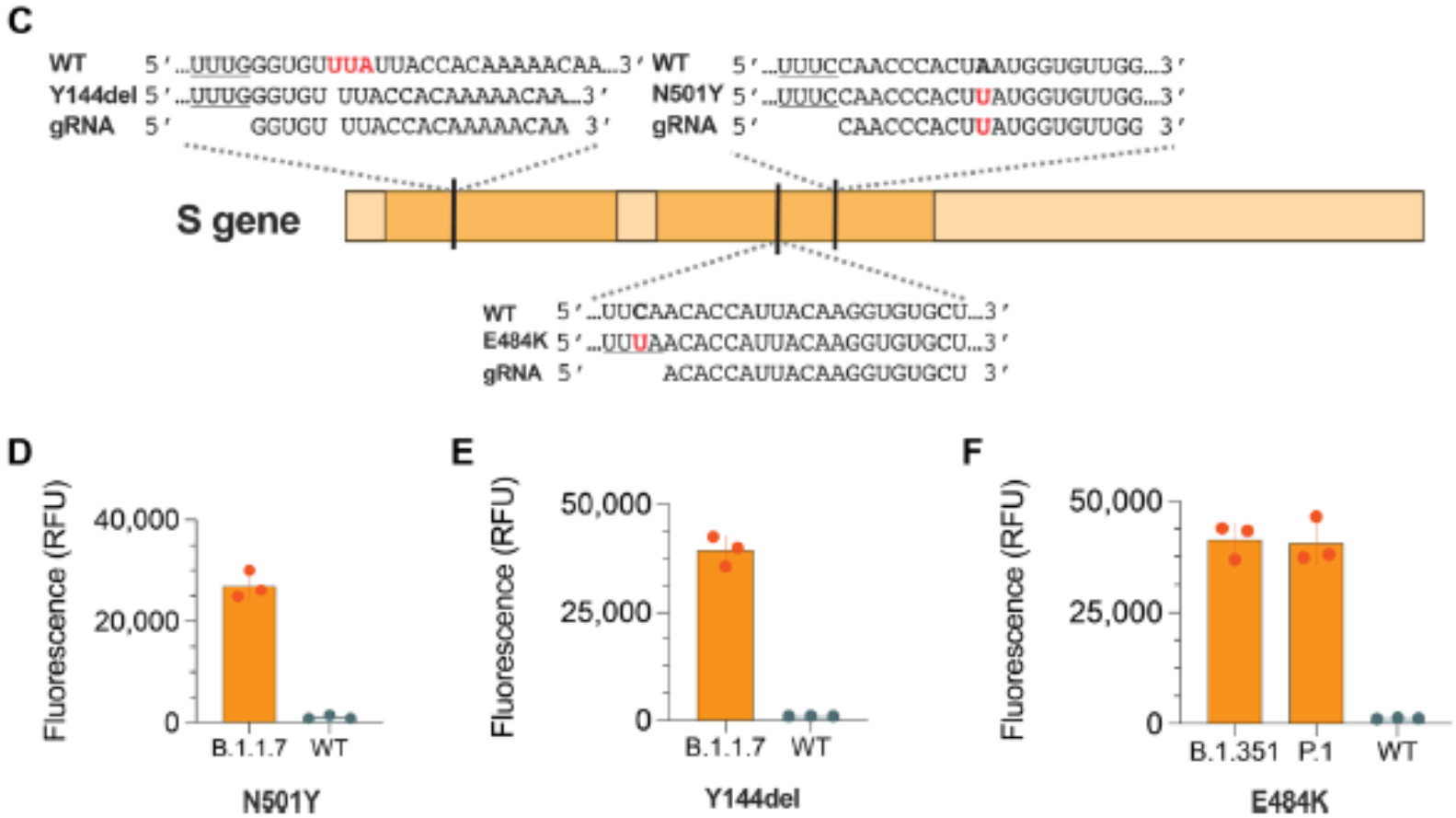
SARS-CoV-2 and variants can be identified with SHERLOCK in saliva



B

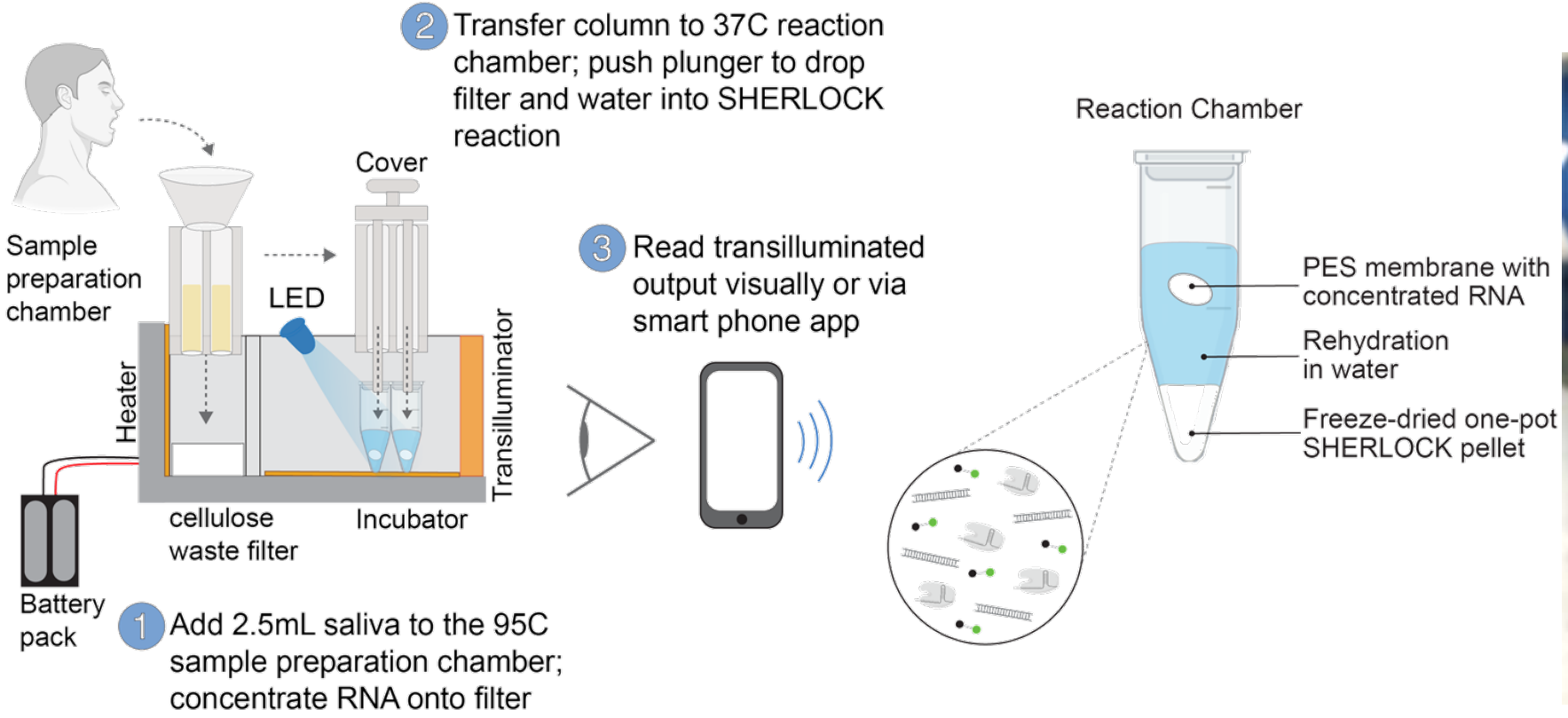
Spike region mutations of the key SARS-CoV-2 variants

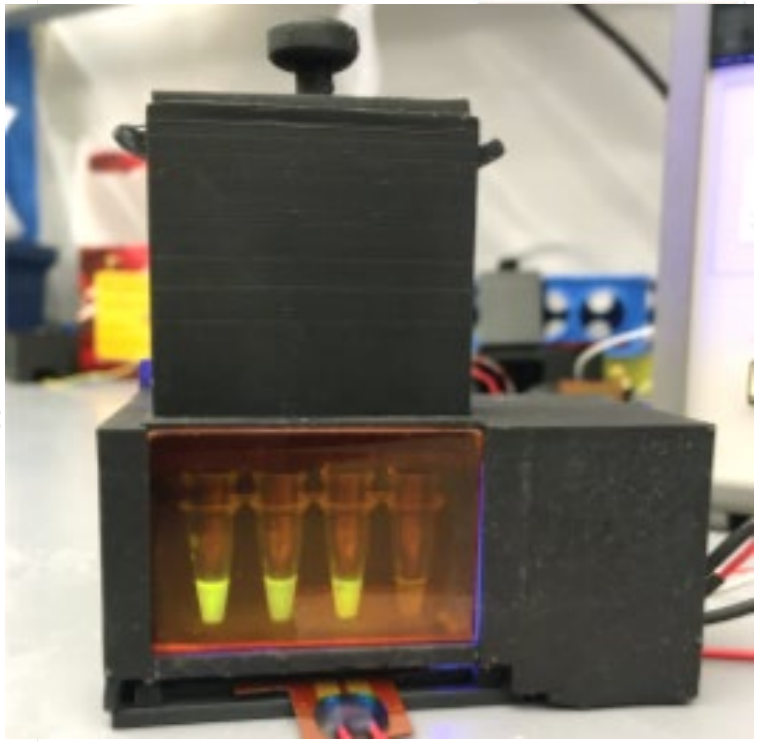
N501Y: A23063T E484K: G23012A	**P.1, B.1.351 (Brazil, S. Africa variant)**
N501Y: A23063T Y144 del: 21991-21993 deletion	**B.1.1.7 (U.K. variant)**



Helena de Puig, … **NE Weckman**…et al. "Minimally instrumented SHERLOCK (miSHERLOCK) for CRISPR-based point-of-care diagnosis of SARS-CoV-2 and emerging variants." *Science Advances* 7.32 (2021): eabh2944.

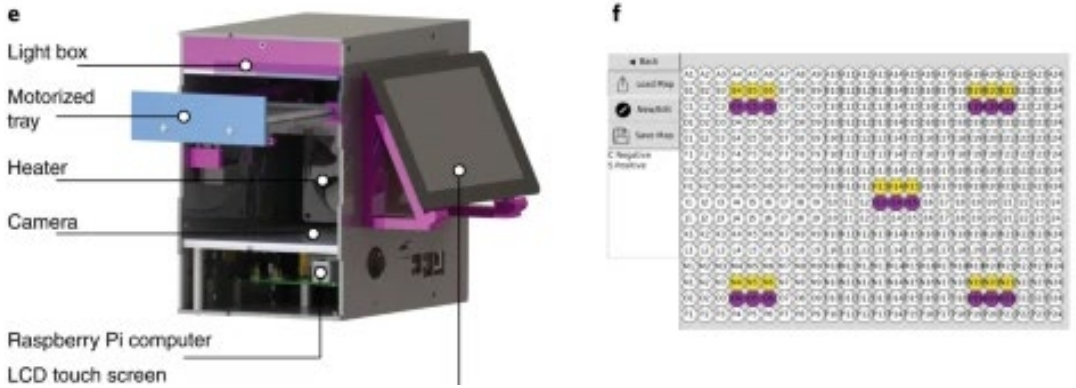
Low-cost, modular, easy-to-use COVID variant detection



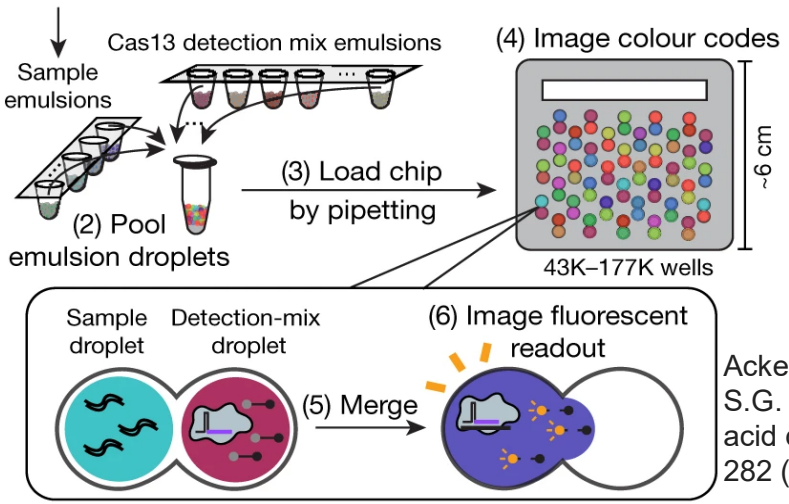


Helena de Puig, … **NE Weckman**…et al. "Minimally instrumented SHERLOCK (miSHERLOCK) for CRISPR-based point-of-care diagnosis of SARS-CoV-2 and emerging variants." *Science Advances* 7.32 (2021): eabh2944.

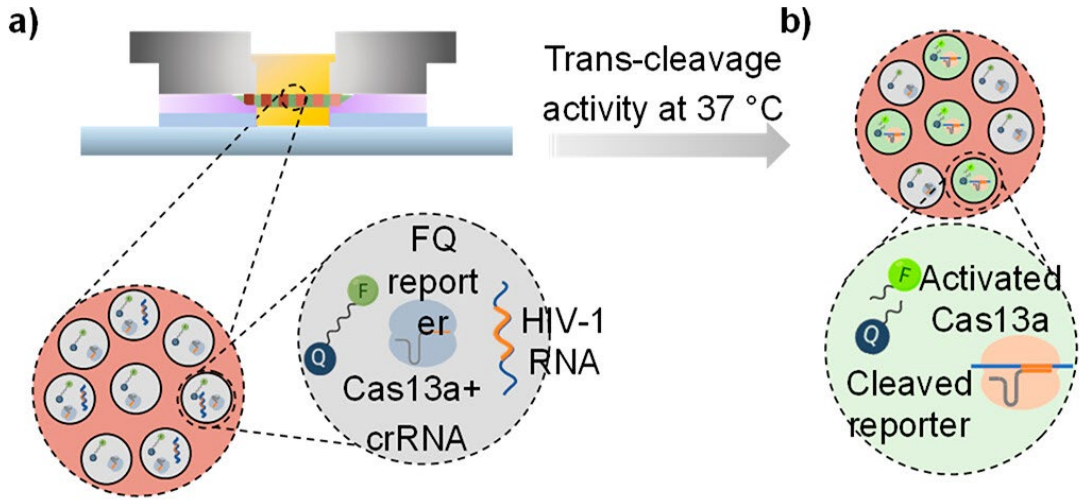
Sample to Result Infectious Disease Diagnostics

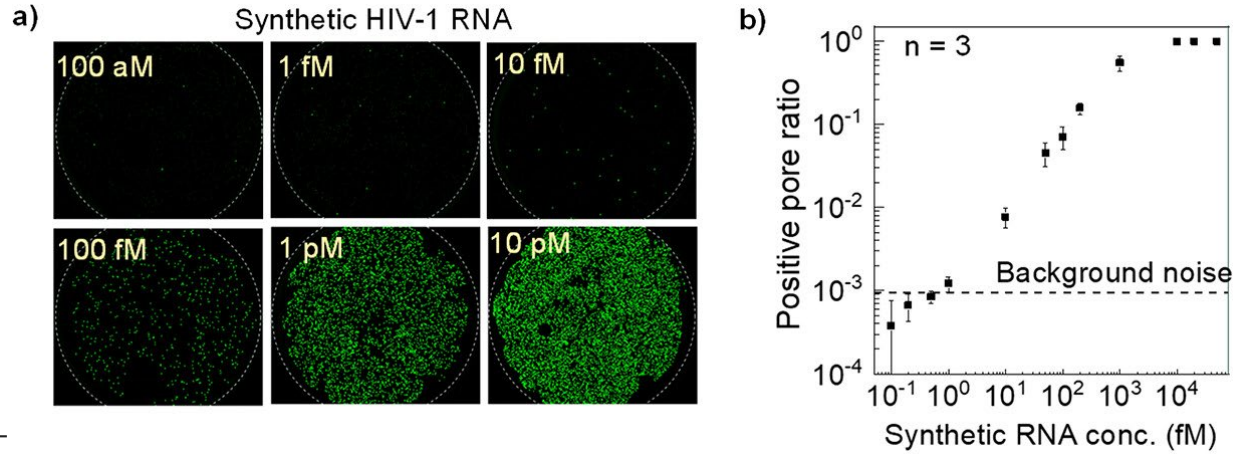


Karlikow, M., *et al.* Field validation of the performance of paper-based tests for the detection of the Zika and chikungunya viruses in serum samples. *Nat. Biomed. Eng* **6**, 246–256 (2022).



Ackerman, C.M., Myhrvold, C., Thakku, S.G. *et al.* Massively multiplexed nucleic acid detection with Cas13. *Nature* **582**, 277–282 (2020).



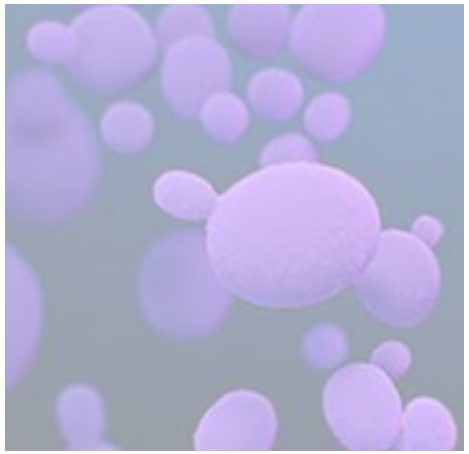


Nouri, Reza, et al. "STAMP-Based Digital CRISPR-Cas13a for Amplification-Free Quantification of HIV-1 Plasma Viral Loads." ACS nano (2023): 512138.

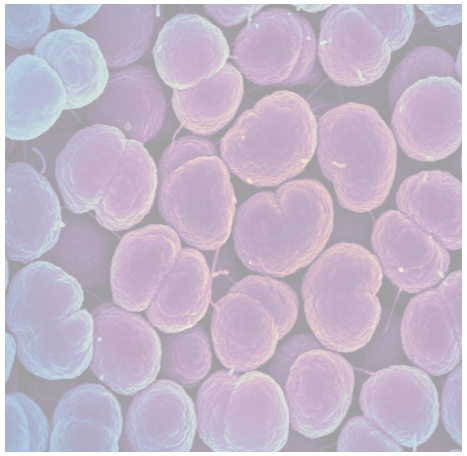
Synthetic biology for sample to answer bioanalysis

Multiplexed and quantitative micro & nanoscale transducers

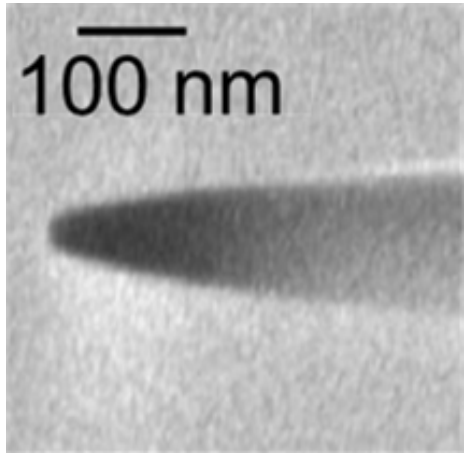
Commercial & User Centered Design



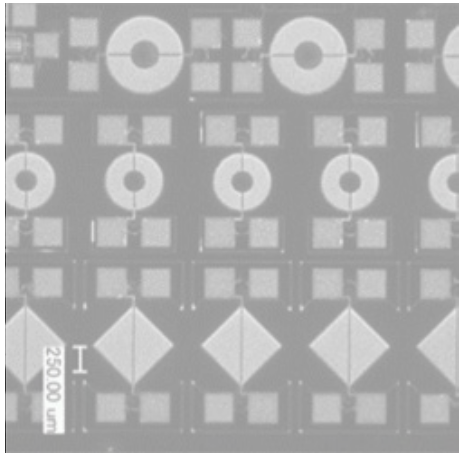
Antifungal Resistance:
Candida Auris



STI Resistance:
N. gonorrhoea



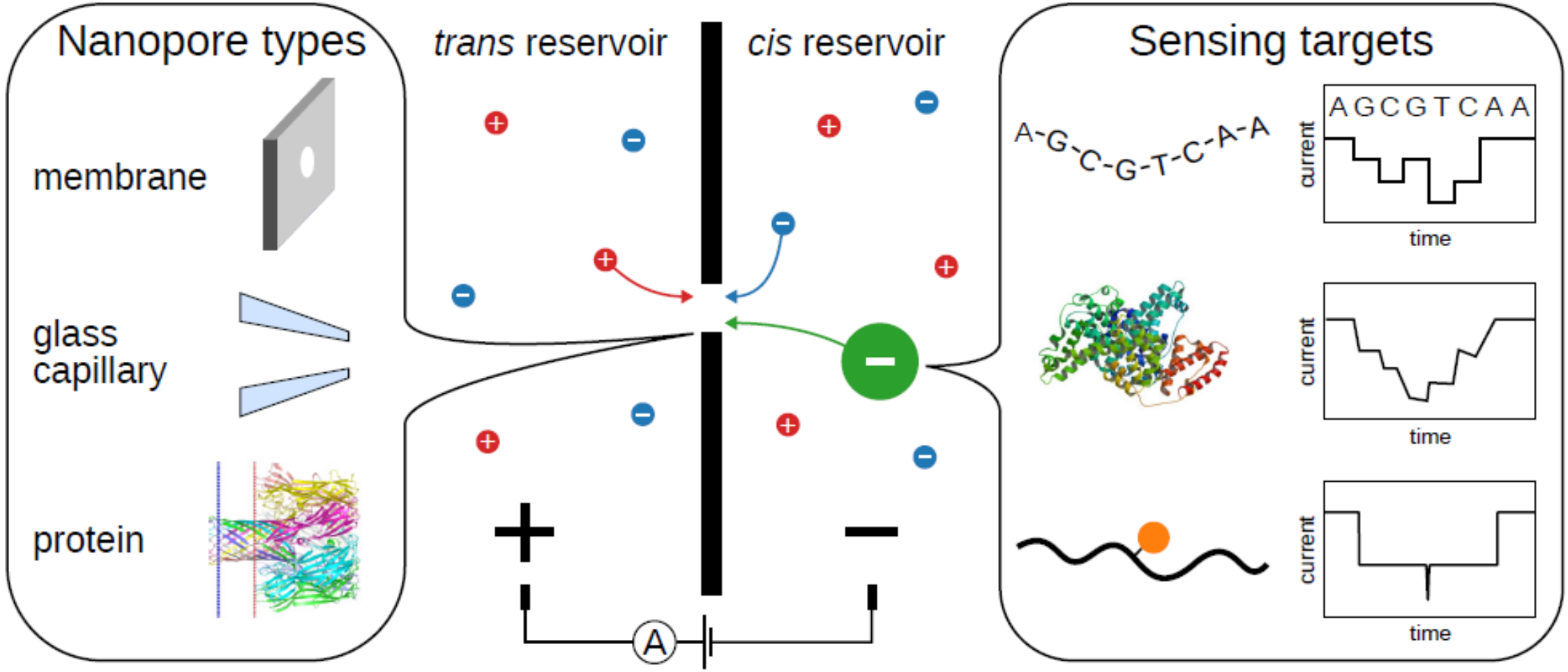
Nanopores



MEMS resonators

POC testing

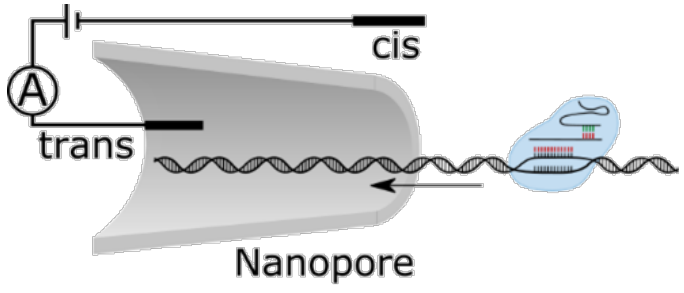
Photo Credit CDC, NIH

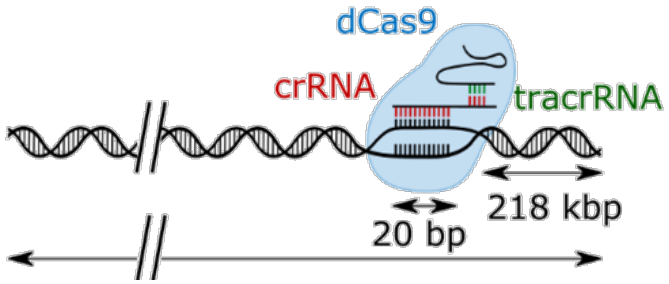


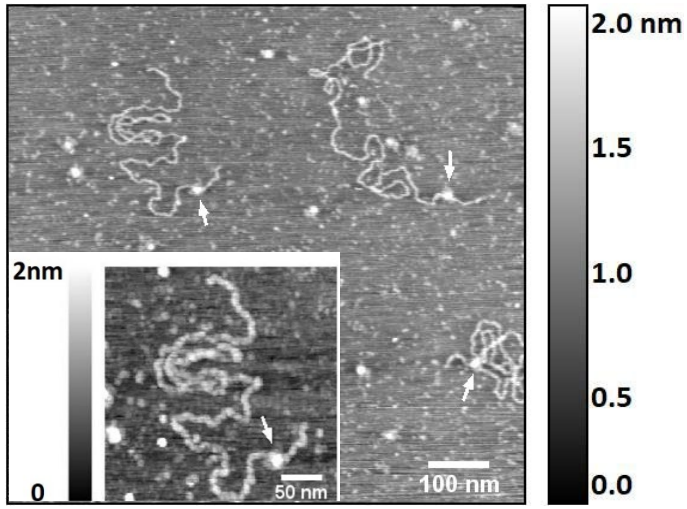
Ermann, Niklas. Nanopore-Based Readout of Encoded DNA Nanostructures. Diss. University of Cambridge, 2020.

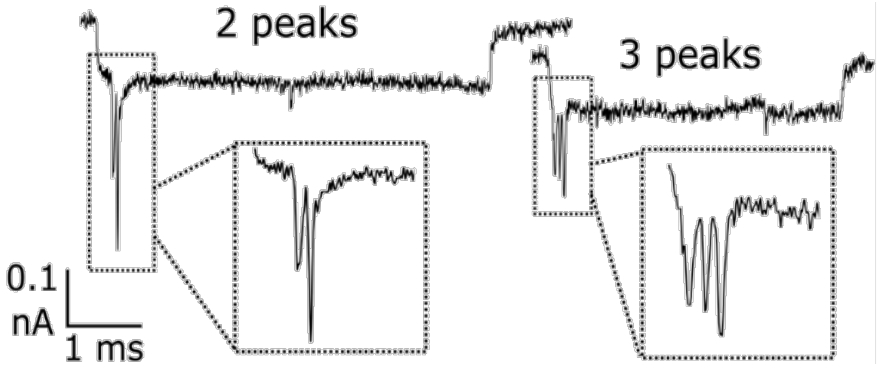
Rapid DNA Identification using dCas9 Barcodes

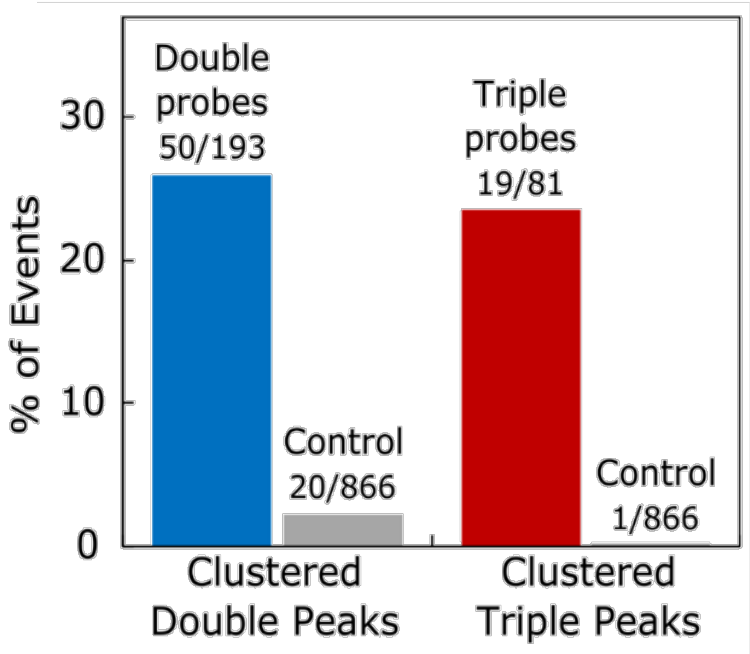
Decorating DNA with dCas9 Barcodes in Nanopores



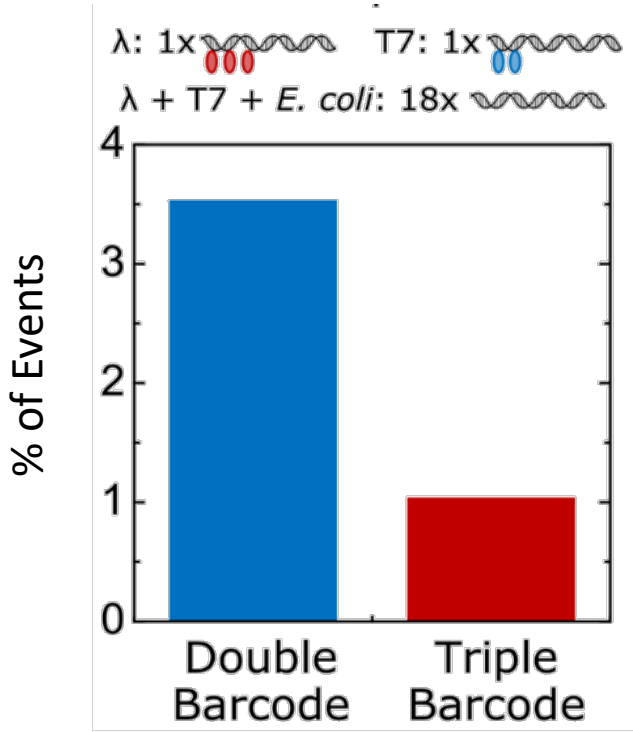






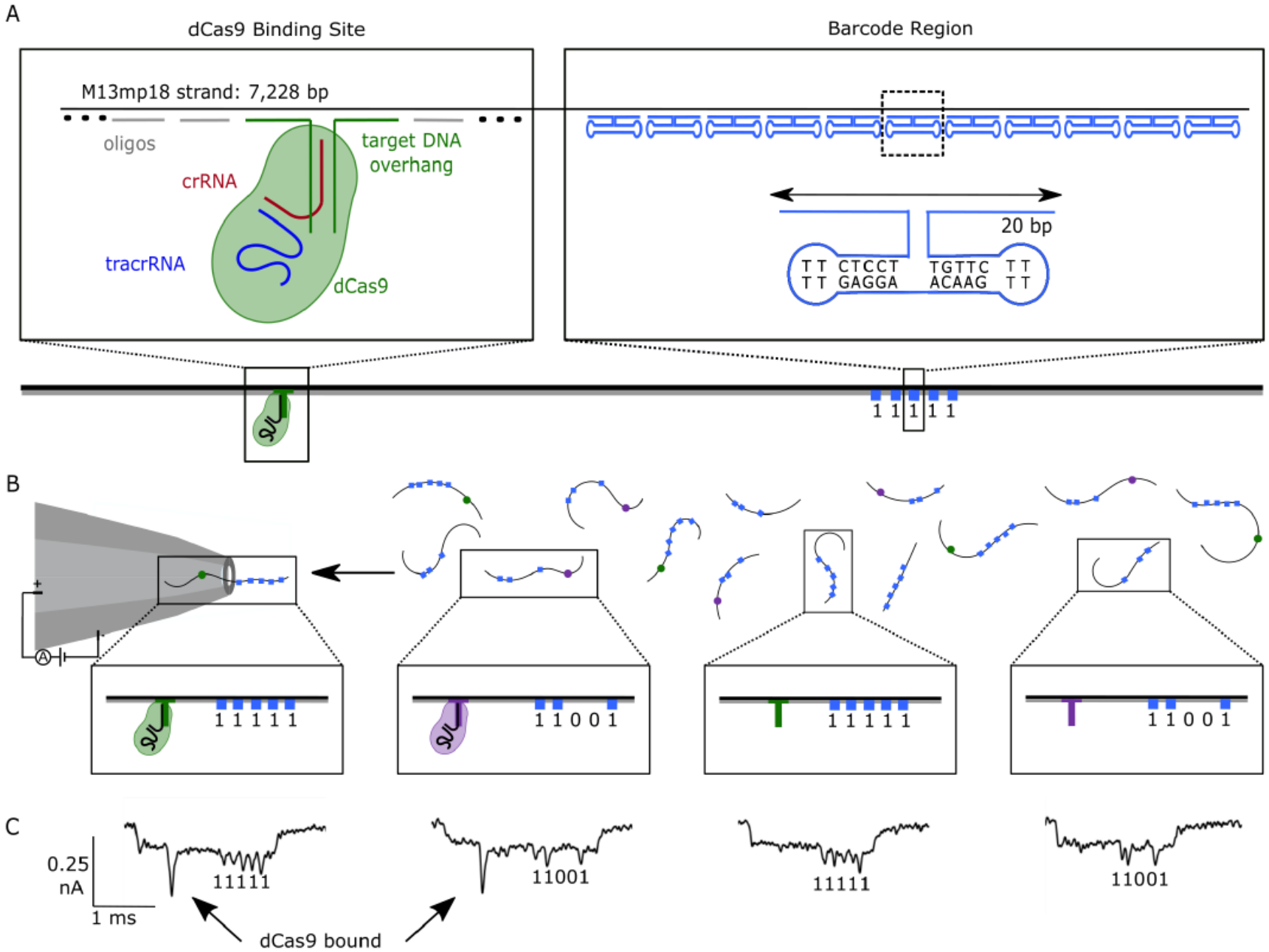


Multiplexing

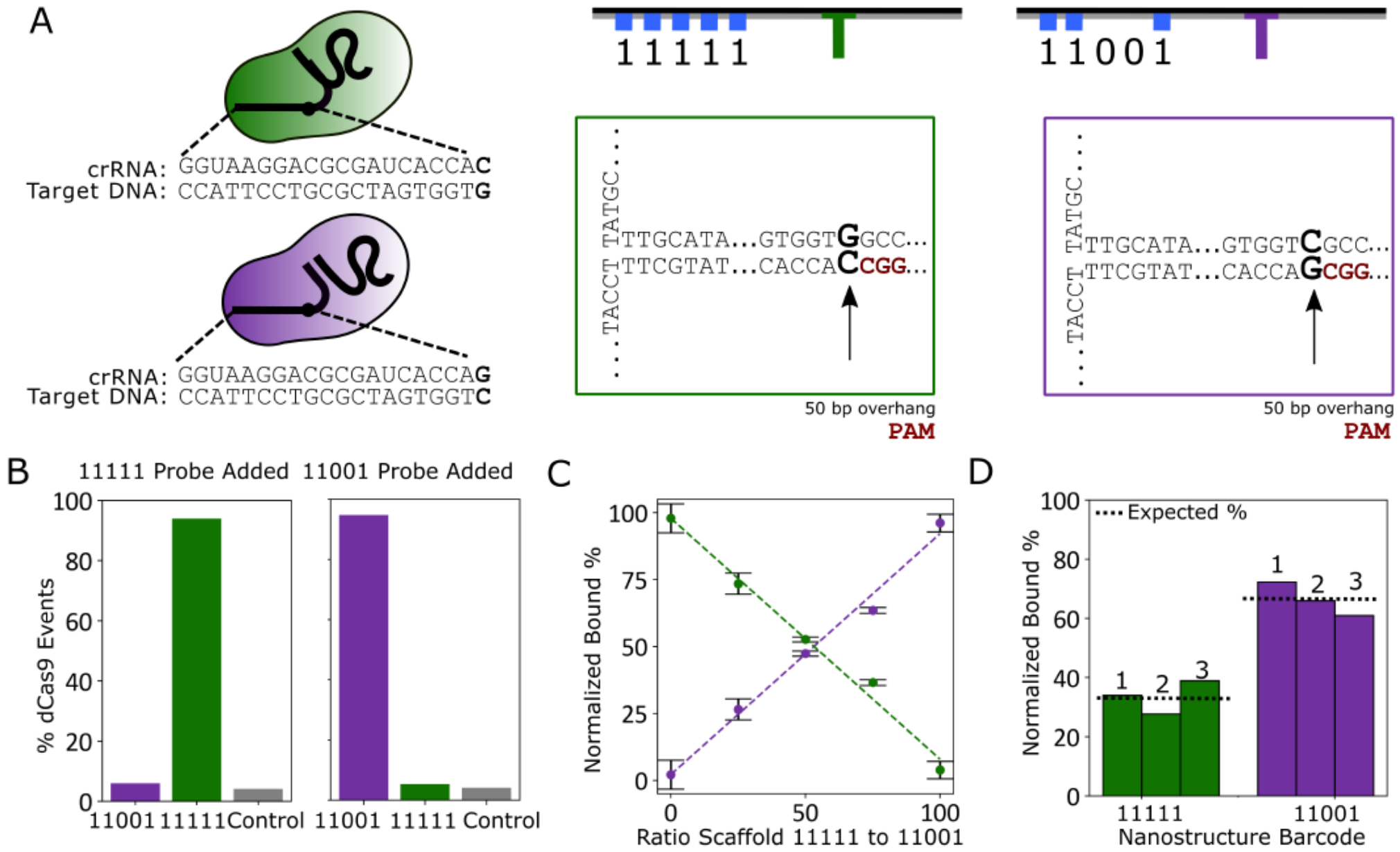


How can we design and test better barcodes?

NE. Weckman, et al. "Multiplexed DNA identification using site specific dCas9 barcodes and nanopore sensing." *ACS sensors* 4.8 (2019): 2065-2072.

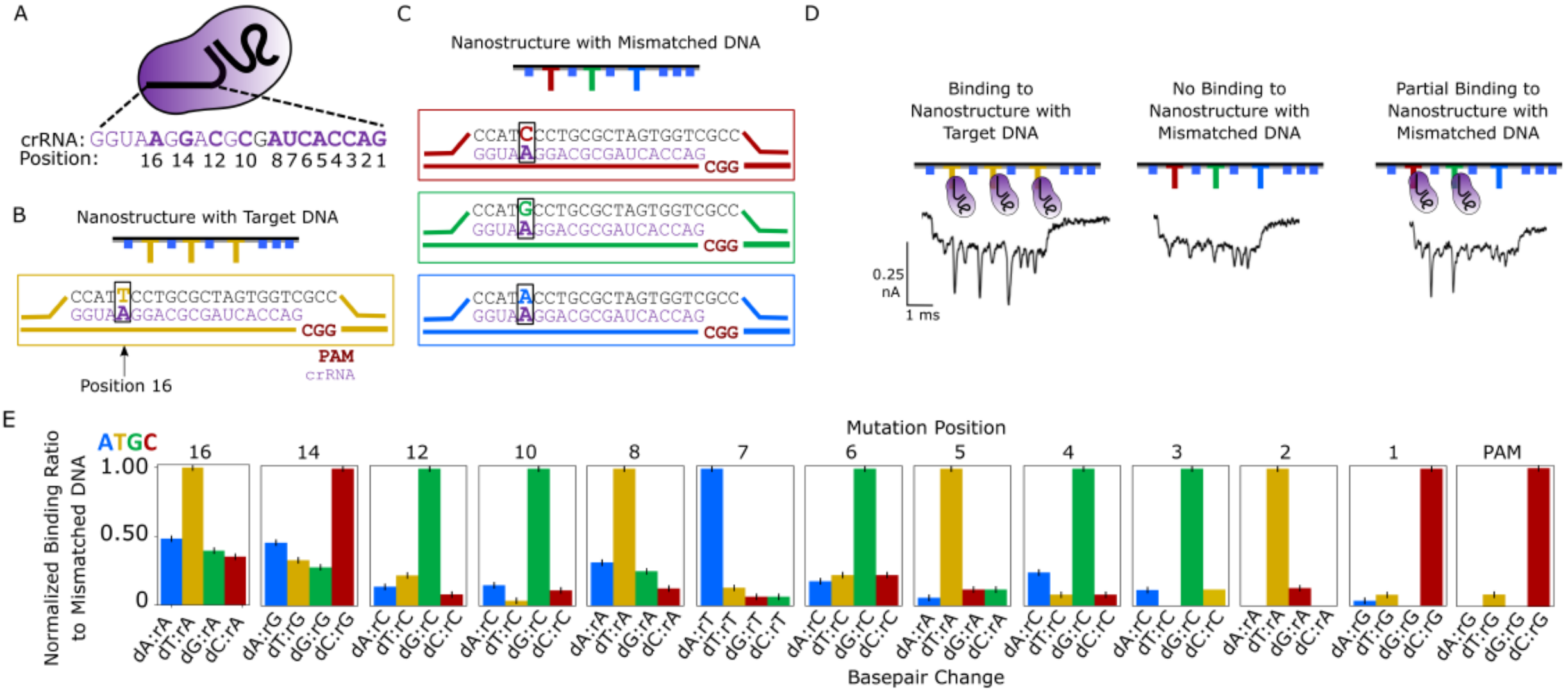


S.E.Sandler, **N.E Weckman**…U.F. Keyser. Sensing the DNA-mismatch tolerance of catalytically inactive Cas9 via barcoded DNA nanostructures in solid-state nanopores. Nature Biomedical Engineering, (2023): 1-10.



S.E.Sandler, **N.E Weckman**…U.F. Keyser. Sensing the DNA-mismatch tolerance of catalytically inactive Cas9 via barcoded DNA nanostructures in solid-state nanopores. Nature Biomedical Engineering, (2023): 1-10.

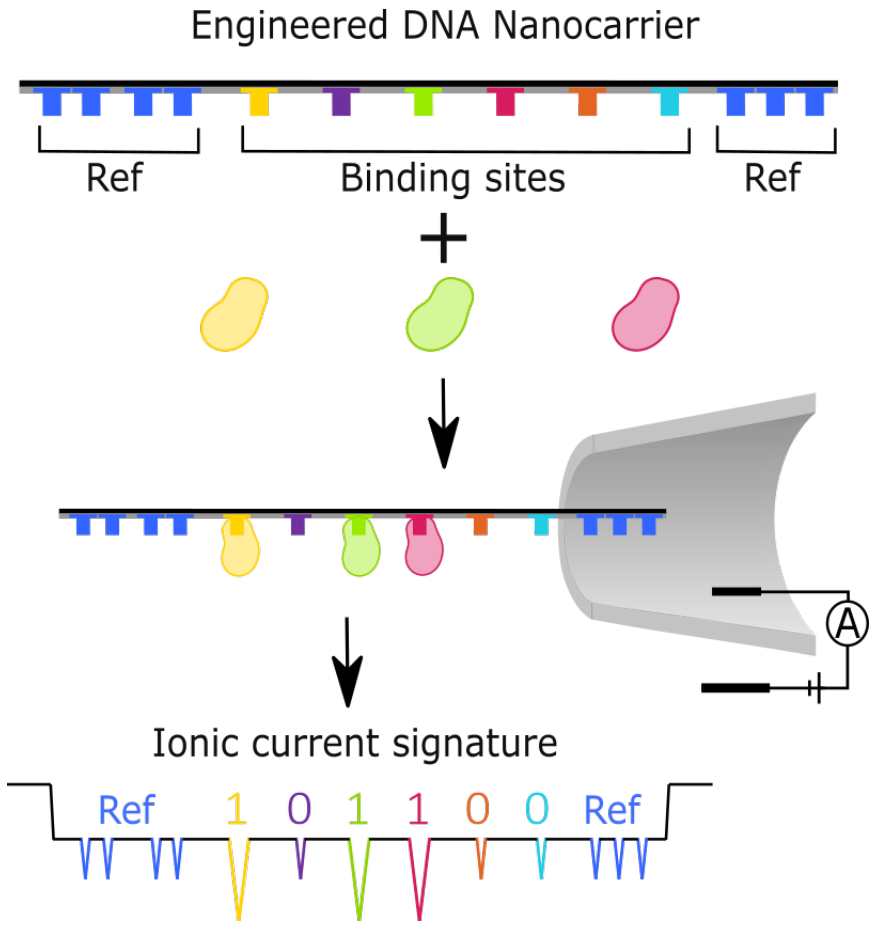
High throughput screening for detection of mutations



S.E.Sandler, **N.E Weckman**…U.F. Keyser. Sensing the DNA-mismatch tolerance of catalytically inactive Cas9 via barcoded DNA nanostructures in solid-state nanopores. Nature Biomedical Engineering, (2023): 1-10.

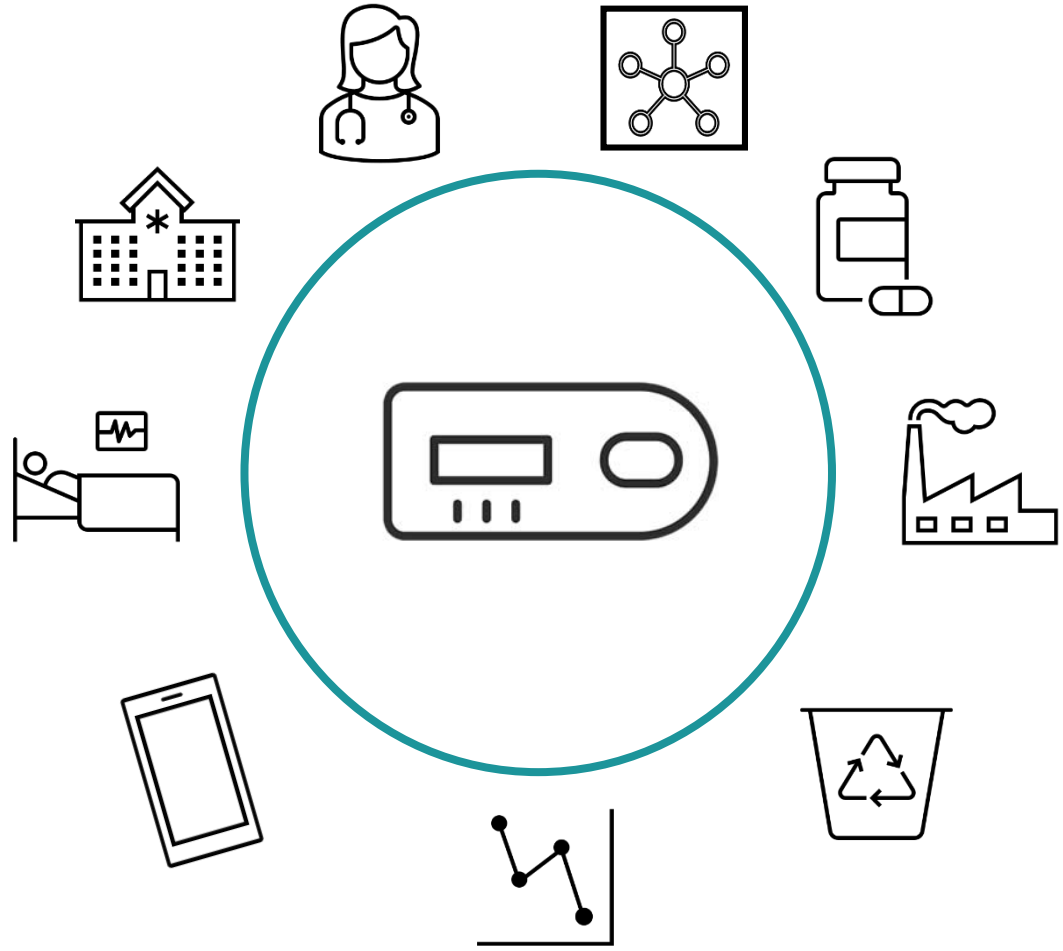
Information storage in DNA nanocarrier structures

- We can directly fingerprint DNA sequences for rapid identification using dCas9 barcodes
- We can rapidly screen DNA protein interactions like dCas9 sensitivity to mutations
- Highly scalable information storage: can we use this for multiplexed sensing of many biomarkers?

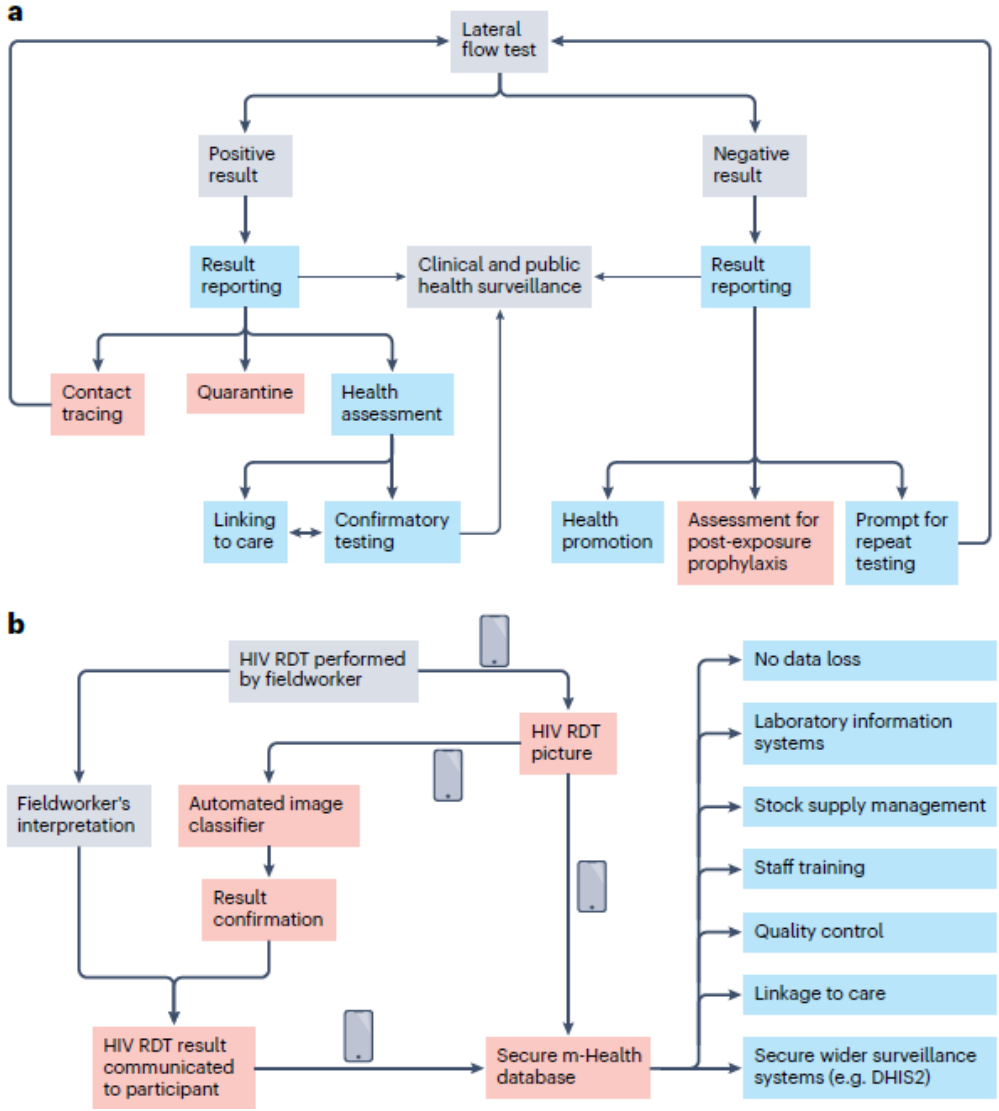


Translation of integrated sensor systems: Bench to Bedside

1. Co-creation with clinical experts, patients, including clinical pathway development
2. Automated result analysis and digital platforms for improved surveillance
3. Design for commercialization and sustainable manufacturing
4. Policy recommendations for decreased regulatory hurdles



Diagnostic devices never exist on their own



Human factors in healthcare IT: Management considerations and trends

Andre W. Kushniruk, MSc, PhD and Elizabeth M. Borycki, RN, PhD View all authors and affiliations

Volume 36, Issue 2 | https://doi.org/10.1177/08404704221139219

Usability problem	Example
Visibility problem	User (e.g. physician) is unable to see an alert presented by an electronic record user interface, as it is not prominently displayed[16]
Understandability problem	User does not understand the onscreen instructions for patient treatment options[16]
Unclear log on/off	User is not sure if they have logged off as the status of the system is not clearly indicated in the user interface[4]
Documenting on the wrong patient record	User is unable to determine what patient they are documenting on due to multiple records open, and as a result inadvertently enters data into the wrong patient record[7]
Navigational problem	User is unable to see how to navigate through a complex set of computer screens to get to a desired screen and section of the system[17]

A comparative analysis of non-invasive prenatal testing in Ontario and Quebec: the role of governing style in health technology innovation & adoption

Lena Saleh, Gillian Parker, Michael Stevenson & Fiona A. Miller

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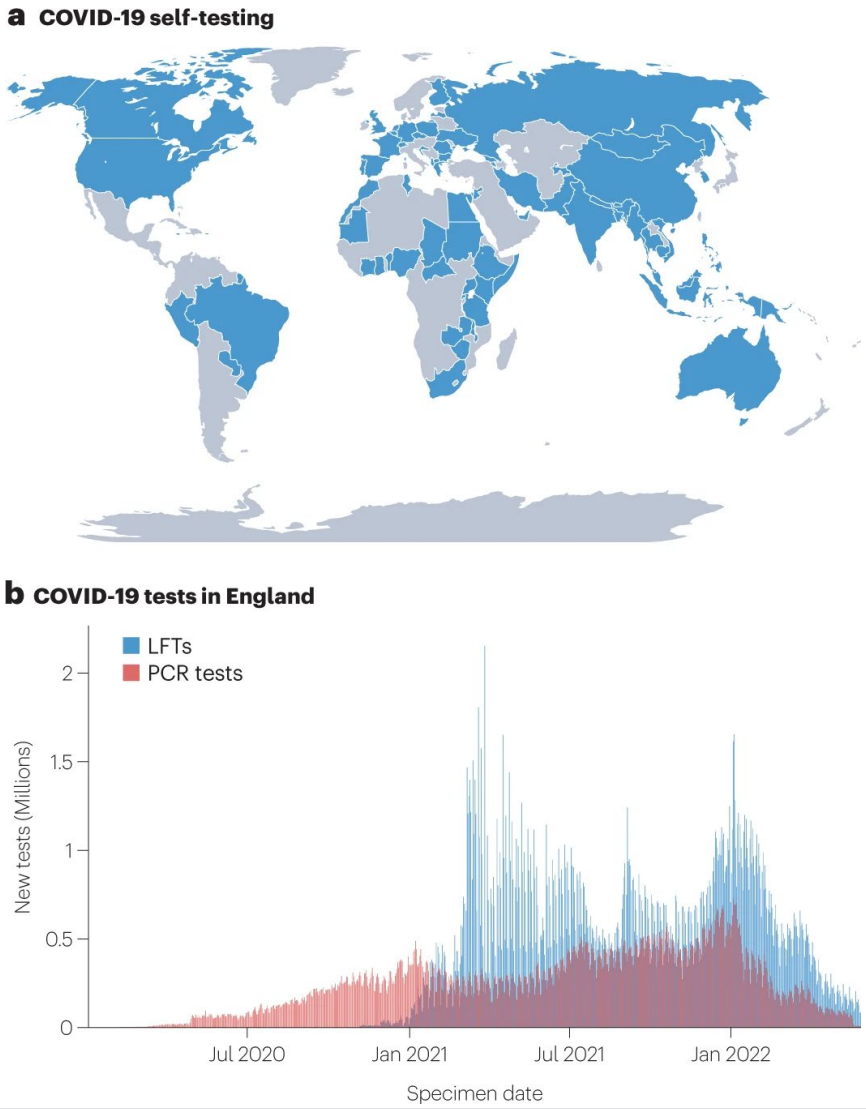
The pandemic has sparked a renaissance in the diagnostics field

- Decentralization of healthcare
- Diverse diagnostic use cases
- Equity in diagnostic access
- Sustainable production
- (Record levels of investment)



Budd, J., Miller, B.S., **Weckman, N.E.** *et al.* Lateral flow test engineering and lessons learned from COVID-19. *Nat Rev Bioeng* **1**, 13–31 (2023).

Useful further reading:
Fleming, Kenneth A., et al. "The Lancet Commission on diagnostics: Transforming access to diagnostics." The Lancet 398.10315 (2021): 1997-2050.

Innovative sensor technologies will lay the foundation for sustainable and equitable global systems

Next Generation Sensors

-Will have an impact on health, the environment, agriculture & food safety, biomanufacturing

Clinically Validated Infectious Disease Diagnostics

- Will improve AMR stewardship
- Will support more equitable healthcare

Research will Engage and Empower Diverse

- Users of sensors
- Students
- Citizen science

"A correct diagnosis is three-fourths the remedy"

~Mahatma Gandhi

Have an idea of an unmet diagnostic need?

Want to chat about fun science?

Reach out: weckmanlab.com, Twitter: @nikkiweckman

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