

# Mass-deployable Molecular Diagnostics (MDx), including COVID-19 Testing: An IC Designer's Perspective

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InSilixa, Inc.

# ~~Brave~~ New World

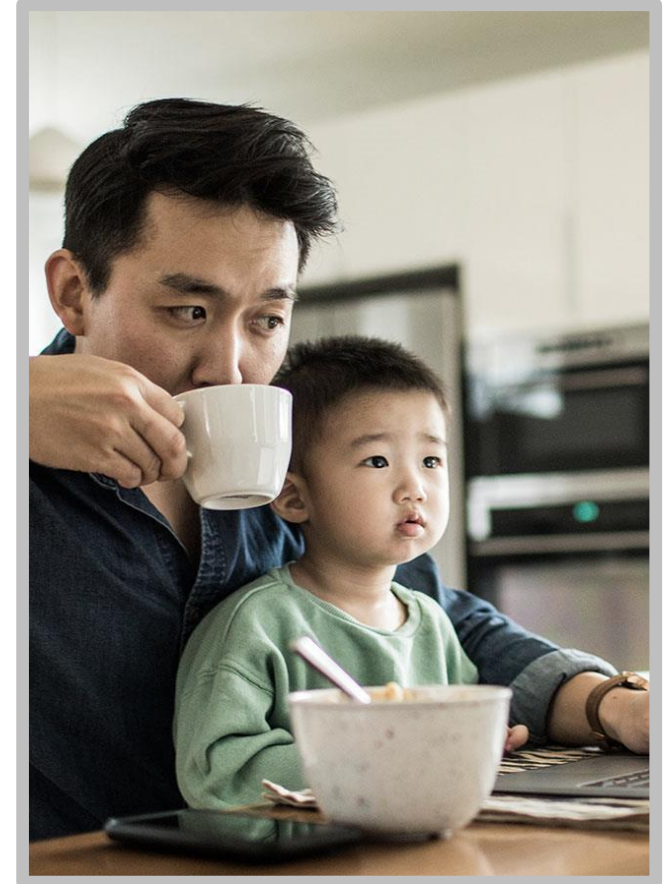
STRANGE



No toilet paper



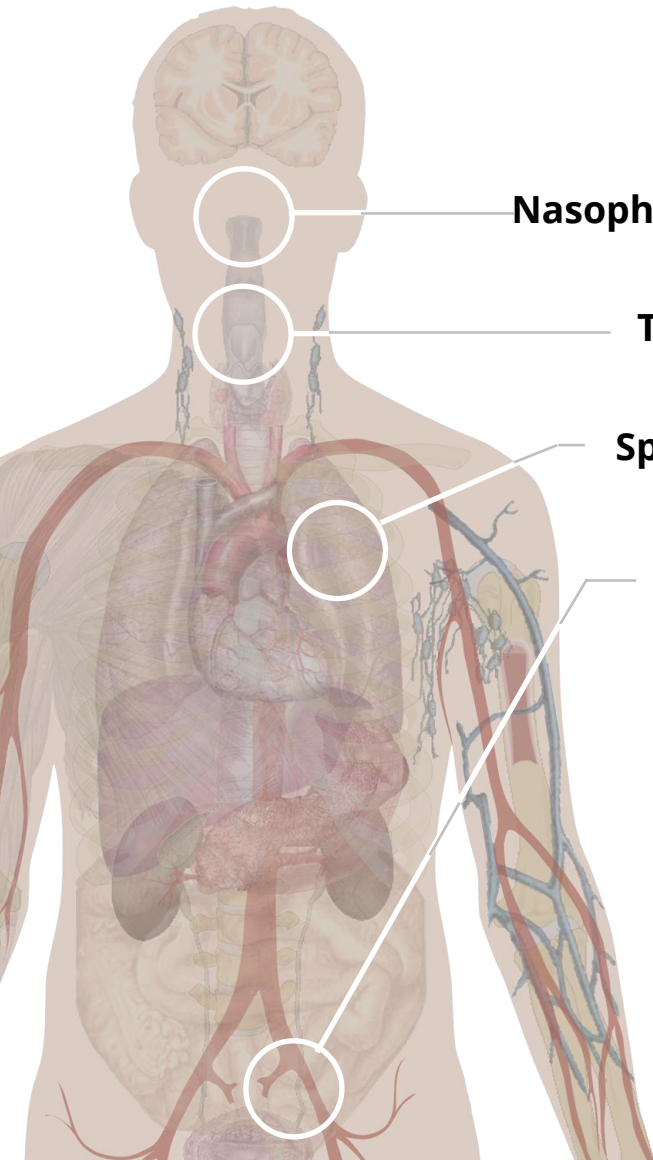
Masks for everyone



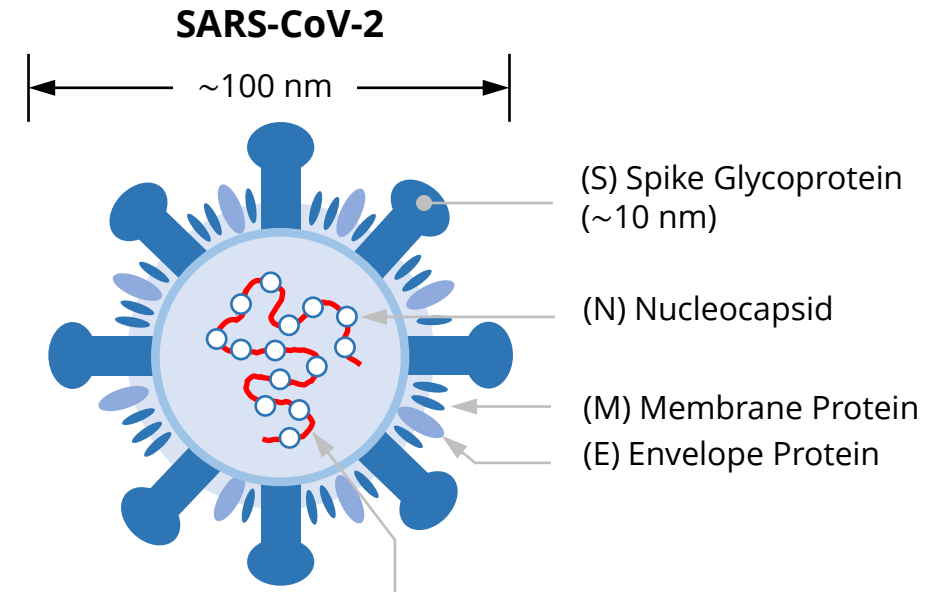
New co-workers

# COVID-19 Detection

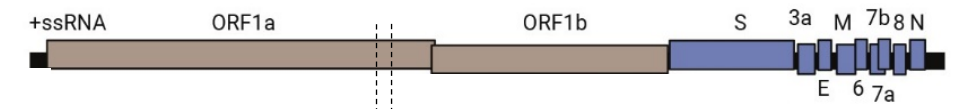
# What are we detecting?



	<u>Infected (Onset)</u>	<u>Infected (Symptoms)</u>	
Nasopharynx	$< 10^3$	$10^6-10^9$	RNAs/swab
Throat	$< 10$	$10^4-10^8$	RNAs/swab
Sputum	-	$10^4-10^8$	RNAs/g
Stool	-	$10^6-10^{11}$	RNAs/ml



RNA Sequence (~30,000 nts)

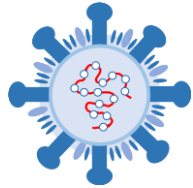


```

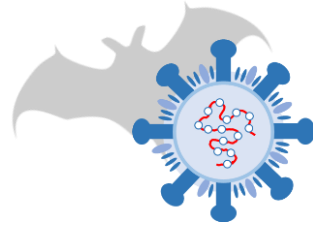
... UGCAUAAUGUGGUUGGACCAUCCAAUGCCGGGUAGU
UAGAUUAGCCCCGCAAAUCAUCUAUGUAGCAUUGGUG
GUGAUCAUACAAAUUCGGCAGCGUGGUCCUUCGA ...
    
```

# What is unique?

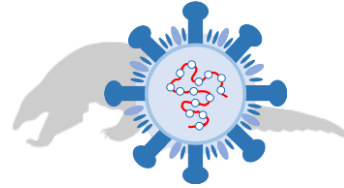
SARS-CoV-2  
(COVID-19)



Bat CoV



Pangolin CoV



SARS-CoV-1



MERS



Common  
Cold CoV



Comparison to SARS-CoV-2 Reference (REF) Sequence

99.9%

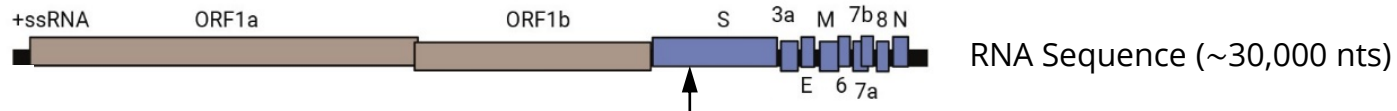
96%

91%

80%

55%

50%



Organism	Strain	Seq. Entries	Sequence
SARS CoV-2	REF.	15670	CTATGGCAATCAAGCCAGCTATAAAACCTAGCCAAATGTACCATGGCCATTTTATATACTGCTCATACTTTCCAAGTTCTTGGAGATCGATGAGAGATTCATT
SARS CoV-2	(Non-REF)	13	CTATGGCAATCAAGCCAGCTATAAAACCTAGCCAAAT <b>A</b> TACCATGGCCATTTTATATACTGCTCATACTTTCCAAGTTCTTGGAGATCGATGAGAGATTCATT
SARS-CoV	REF.	195	C <b>G</b> ATGGCAAT <b>T</b> AG <b>T</b> CCAGC <b>A</b> AT <b>G</b> AA <b>G</b> CC <b>G</b> AGCCAA <b>A</b> CA <b>T</b> ACCA <b>A</b> GGCCATTT <b>A</b> ATATA <b>T</b> GGCTCATA <b>T</b> TTTCC <b>C</b> AA <b>T</b> TCTT <b>G</b> AG <b>G</b> TC <b>A</b> ATGAG <b>T</b> GATTCATT
MERS	REF.	249	CTA <b>A</b> GGCAA <b>C</b> A <b>A</b> GC <b>C</b> AGC <b>A</b> AT <b>G</b> AA <b>A</b> CC <b>A</b> AGCCAAATGTACCA <b>C</b> GGCCATTT <b>G</b> T <b>T</b> G <b>T</b> A <b>A</b> TA <b>A</b> AG <b>A</b> TA <b>A</b> ATT <b>G</b> CCAAG <b>C</b> TCTT <b>T</b> AG <b>G</b> TC <b>T</b> AT <b>G</b> TA <b>A</b> AG <b>C</b> TCATT

# How is COVID-19 detected today?

**GeneXpert**  
(GeneXpert)



**QIAstat-Dx**  
(Qiagen)



**Cobas 8800**  
(Roche)



FDA  
Approved for  
COVID-19

March 21<sup>st</sup>  
2020

10-12 tests  
/bay/8 hours

March 31<sup>st</sup>  
2020

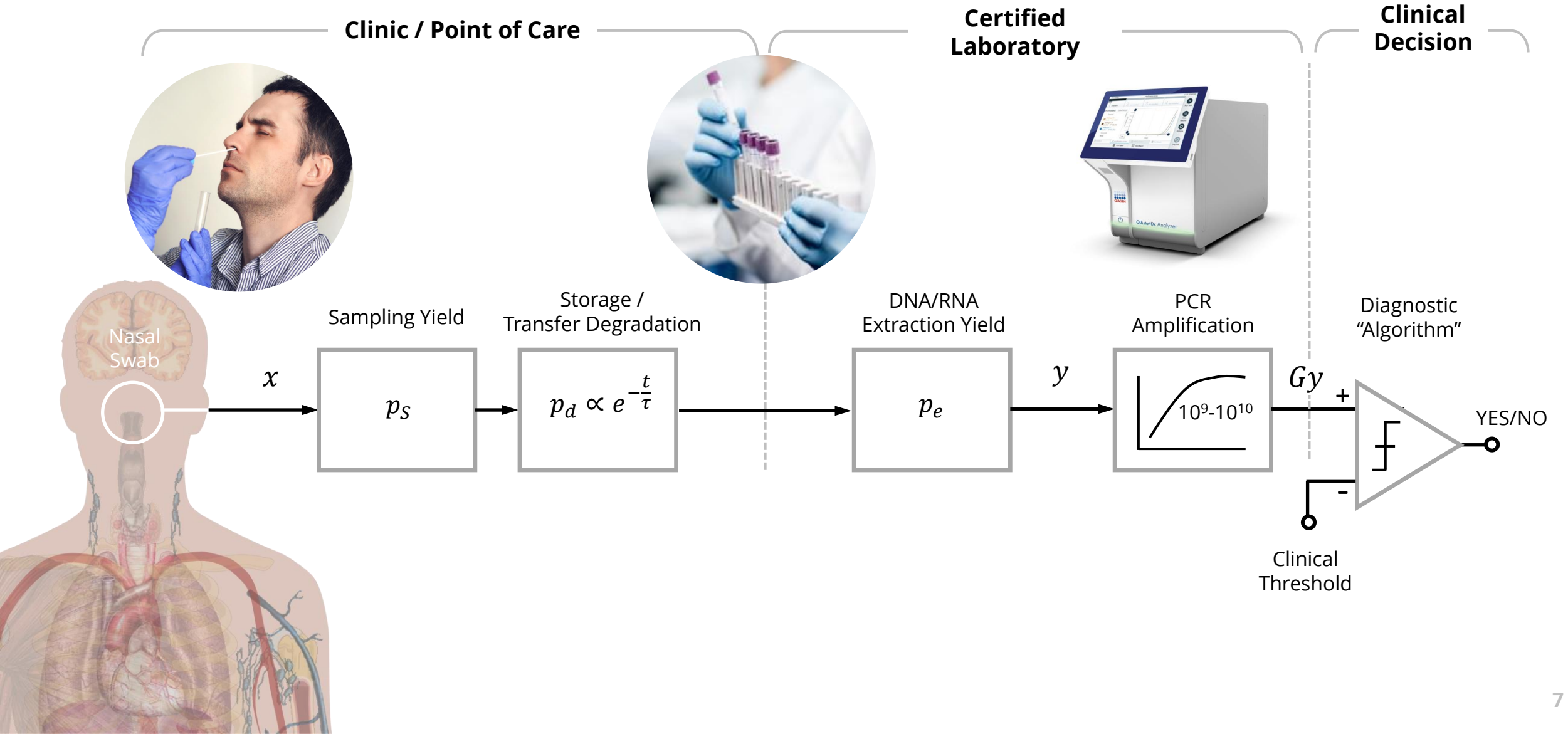
6 tests  
/bay/8 hours

March 13<sup>th</sup>  
2020

1056 tests  
/8 hours

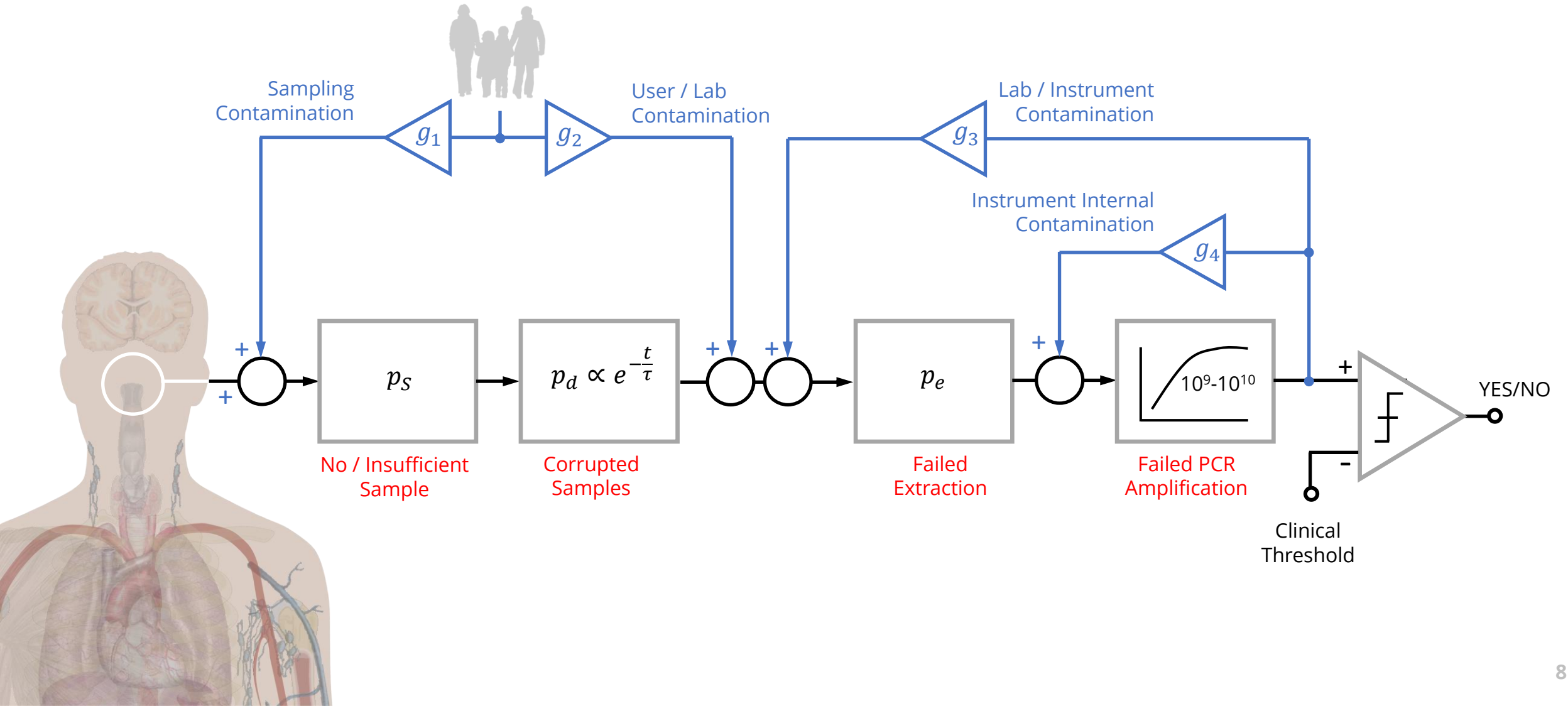
**Molecular Diagnostic (MDx) Systems**

# “Signal chain” for MDx



# Error (noise) sources

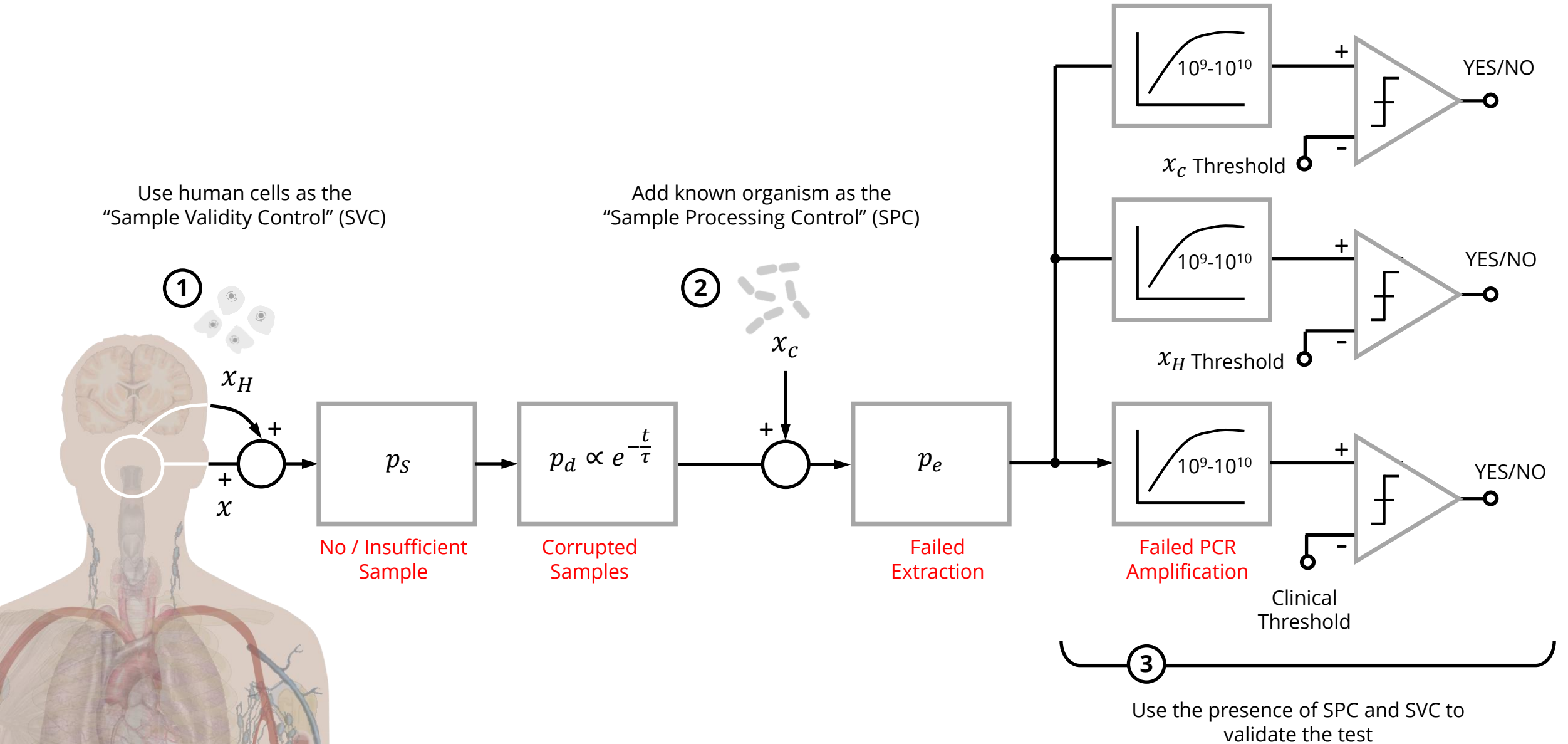
Main category of errors are process nonidealities (—) and contaminations (—)



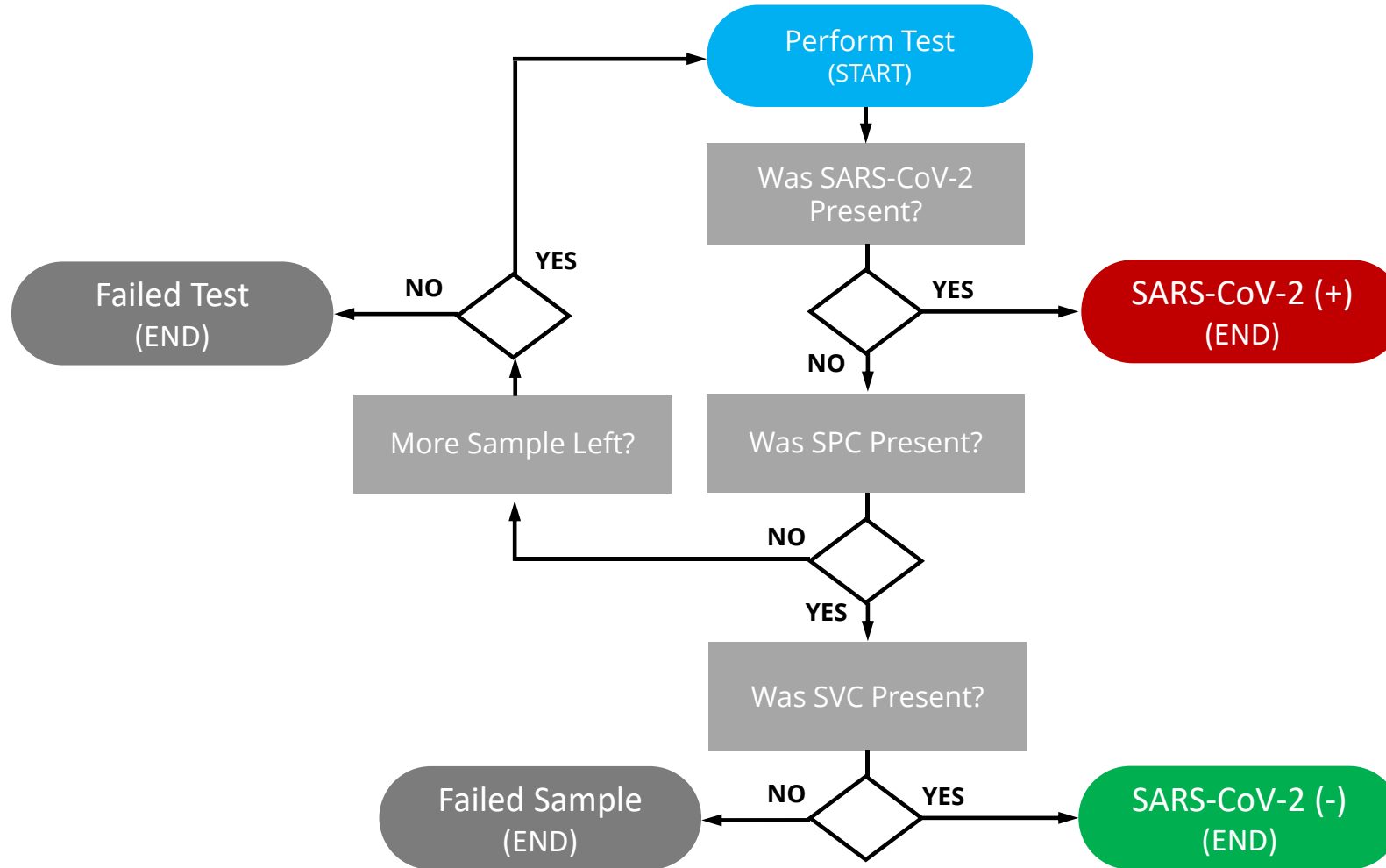




# Addressing errors: Process nonidealities



# Diagnostic algorithm: SARS-CoV-2 (COVID-19) example



# Key question

What if you have flu-like symptoms, but your SARS-CoV-2 (COVID-19) test is negative?

SARS-CoV-2 (-)  
(END)



“What ‘s wrong with me?”

	Organism/Strain	Target	Probability <sup>1</sup>
1	Pan Influenza A	(-)RNA Virus	<b>22.7%</b>
2	Influenza A Type H1		
3	Influenza A Type H3		
4	2009 Pandemic H1N1 Influenza A		
5	Influenza A Antiviral Resistance Starin		
6	Pan Influenza B	(-)RNA Virus	<b>16.1%</b>
7	Pan Respiratory Syncytial Virus (RSV)	(-)RNA Virus	<b>13.5%</b>
8	Parainfluenza Virus 1	(-)RNA Virus	<b>8%</b>
9	Parainfluenza Virus 2		
10	Parainfluenza Virus 3		
11	Parainfluenza Virus 4		
12	Pan Human Metapneumovirus	(-)RNA Virus	<b>1.2%</b>
13	Adenovirus B DNA virus	DNA Virus	<b>2.7%</b>
14	Adenovirus C DNA virus		
15	Adenovirus E DNA virus		
16	Coronavirus 229E	(+)RNA Virus	<b>8.0%</b>
17	Coronavirus NL63		
18	Coronavirus HKU1		
19	Coronavirus OC43		
20	Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1)		
21	Middle East Respiratory Syndrome-Related Coronavirus (MERS)		
22	Human Enterovirus	(+)RNA Virus	<b>6.1%</b>
23	Human Enterovirus D68		<b>0.1%</b>
24	Human Rhinovirus	(+)RNA Virus	<b>14%</b>
25	<i>M. pneumoniae</i> Bacterium	Bacteria	<b>4.1%</b>
26	<i>C. pneumoniae</i> Bacterium	Bacteria	<b>1.4%</b>
27	<i>B. pertussis</i> Bacterium	Bacteria	<b>1.0%</b>

**TOTAL 98.9%**

<sup>1</sup> Example numbers; the actual numbers are highly dependent on the year and country/region

# Optimal and actionable test

A test that quickly identifies ALL clinically relevant pathogens to enable optimal treatment (if any)

Actionable Test



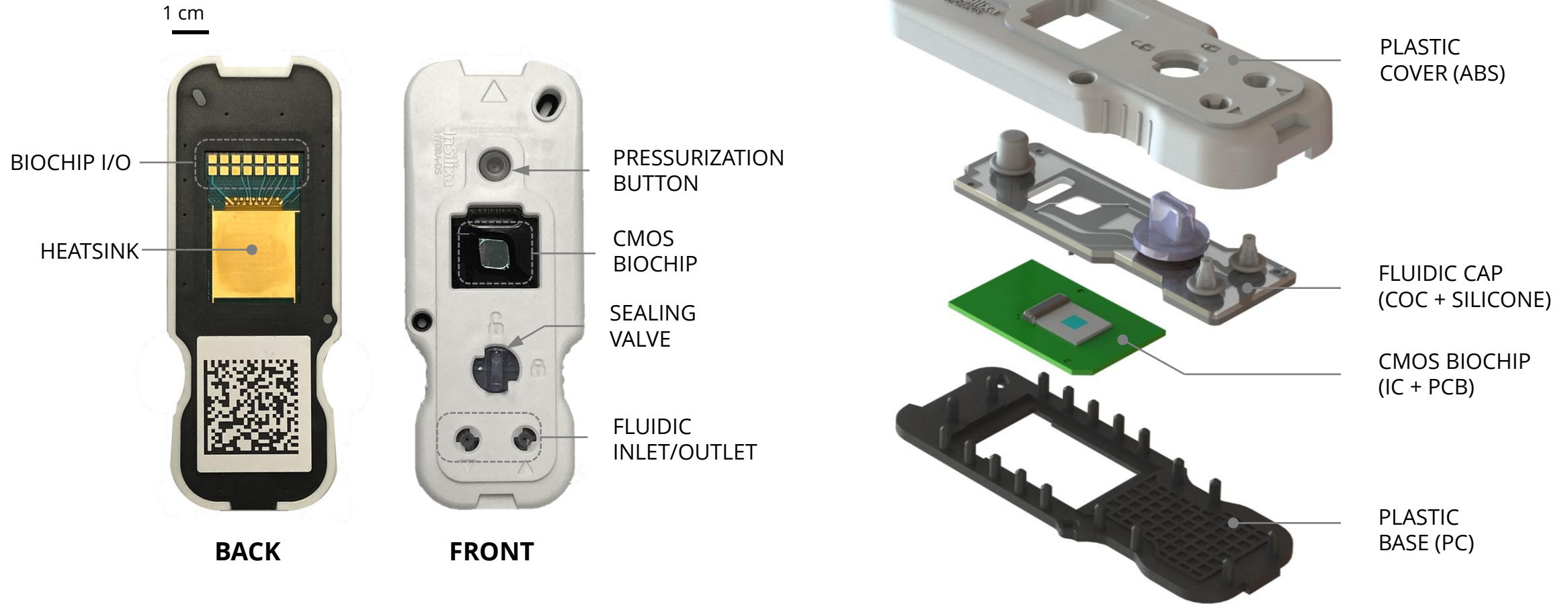
	Organism/Strain	Target	TEST RESULTS
1	Pan Influenza A	(-)RNA Virus	NEG.
2	Influenza A Type H1		NEG.
3	Influenza A Type H3		NEG.
4	2009 Pandemic H1N1 Influenza A		NEG.
5	Influenza A Antiviral Resistance Starin		NEG.
6	Pan Influenza B	(-)RNA Virus	NEG.
7	Pan Respiratory Syncytial Virus (RSV)	(-)RNA Virus	NEG.
8	Parainfluenza Virus 1	(-)RNA Virus	NEG.
9	Parainfluenza Virus 2		NEG.
10	Parainfluenza Virus 3		NEG.
11	Parainfluenza Virus 4		NEG.
12	Pan Human Metapneumovirus	(-)RNA Virus	NEG.
13	Adenovirus B DNA Virus	DNA Virus	NEG.
14	Adenovirus C DNA Virus		NEG.
15	Adenovirus E DNA Virus		NEG.
16	Coronavirus 229E	(+)RNA Virus	NEG.
17	Coronavirus NL63		NEG.
18	Coronavirus HKU1		NEG.
19	Coronavirus OC43		NEG.
20	Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1)		NEG.
21	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)		NEG.
22	Middle East Respiratory Syndrome-Related Coronavirus (MERS)		NEG.
23	Human Enterovirus	(+)RNA Virus	NEG.
24	Human Enterovirus D68	(+)RNA Virus	NEG.
25	Human Rhinovirus	(+)RNA Virus	<b>POSITIVE</b>
26	<i>M. pneumoniae</i> Bacterium	Bacteria	<b>POSITIVE</b>
27	<i>C. pneumoniae</i> Bacterium	Bacteria	NEG.
28	<i>B. pertussis</i> Bacterium	Bacteria	NEG.

# Example CMOS Biochip for COVID-19 Testing

# HYDRA MDx system (InSilixa, Inc.)



# HYDRA biochip module

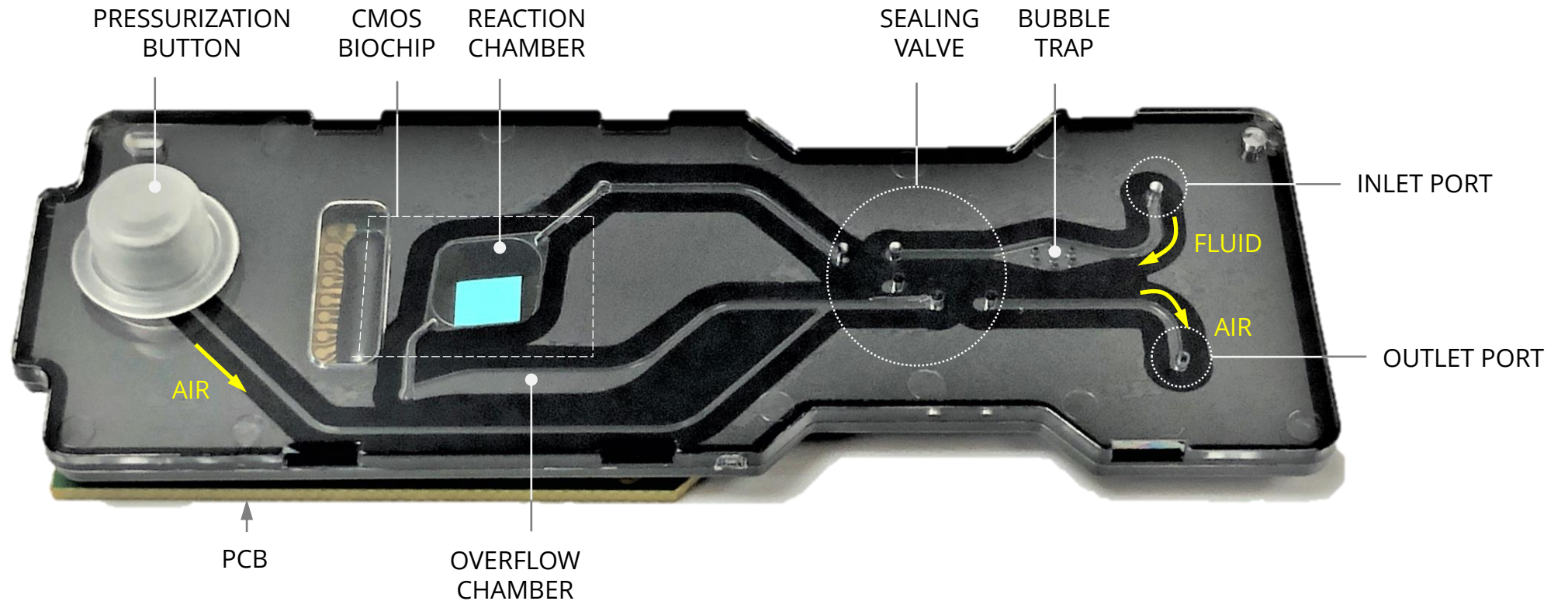




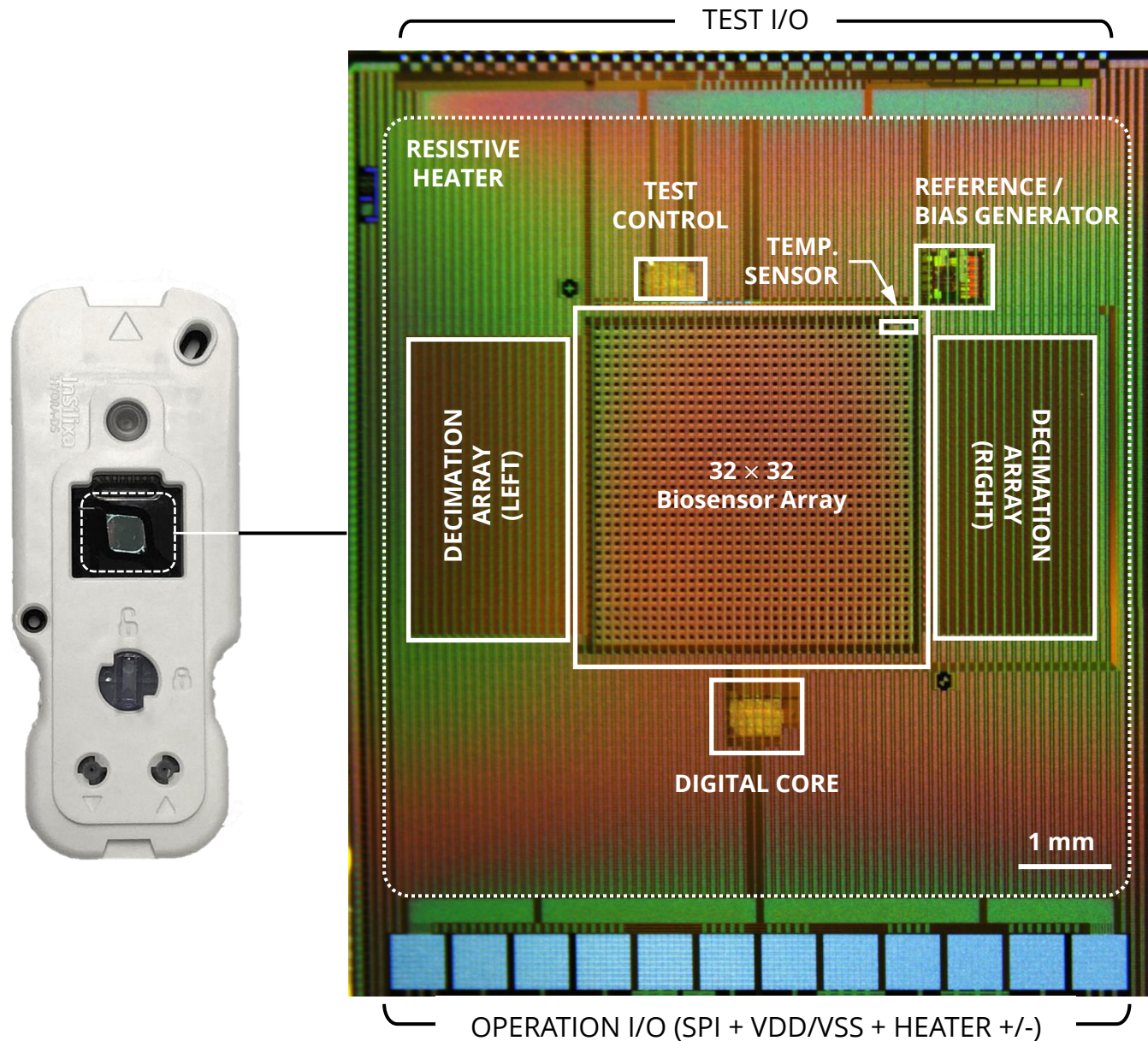
# Biochip fluidics

## STEPS:

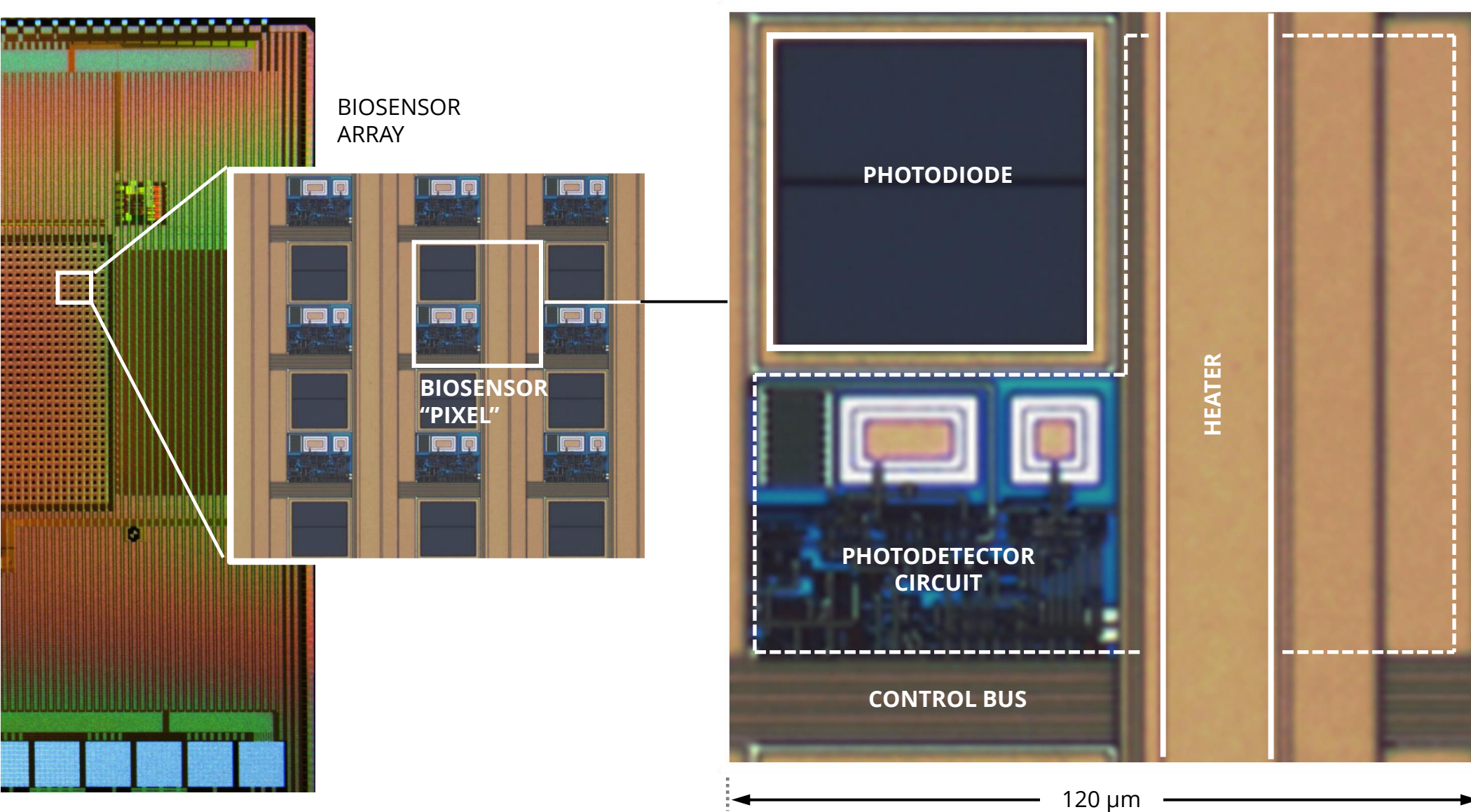
Load Sample → Seal → Pressurize to > 2 bar(g) → Run PCR → Depressurize → Never Unseal



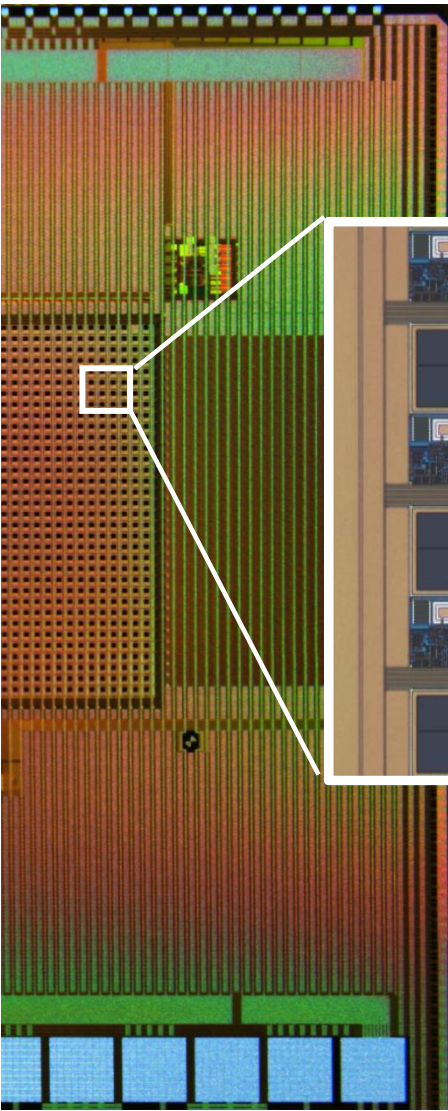
# CMOS biochip: HYDRA-1KS



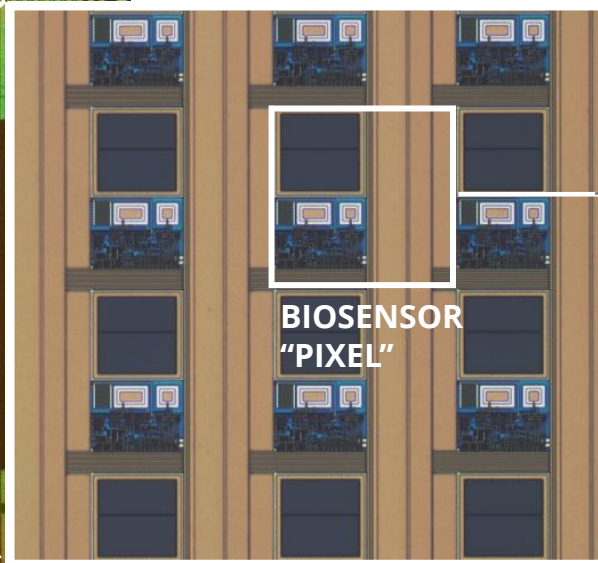
# Biosensor array and biosensor "pixels"



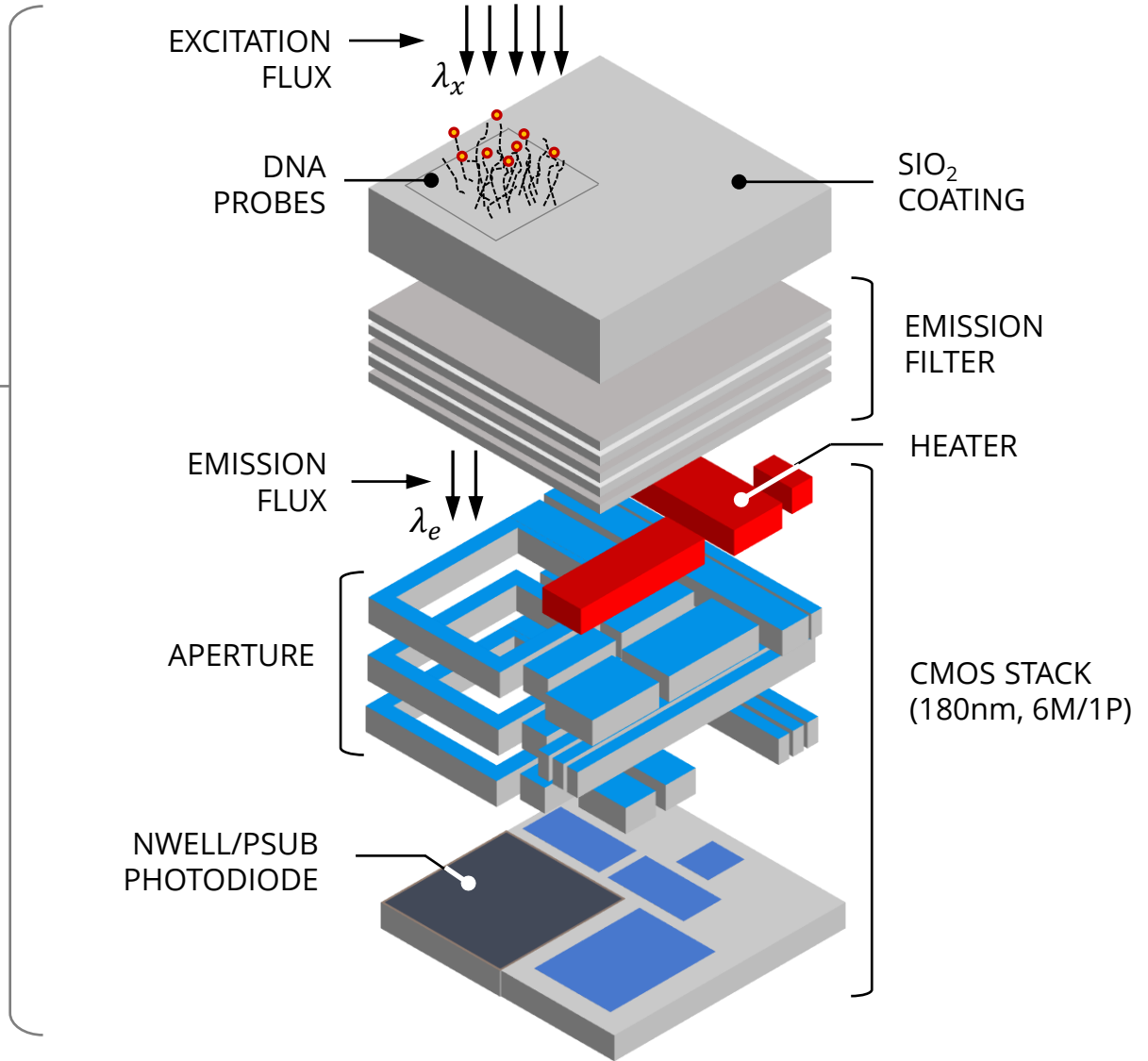
# Material stack of the biosensor "pixel"



BIOSENSOR  
ARRAY

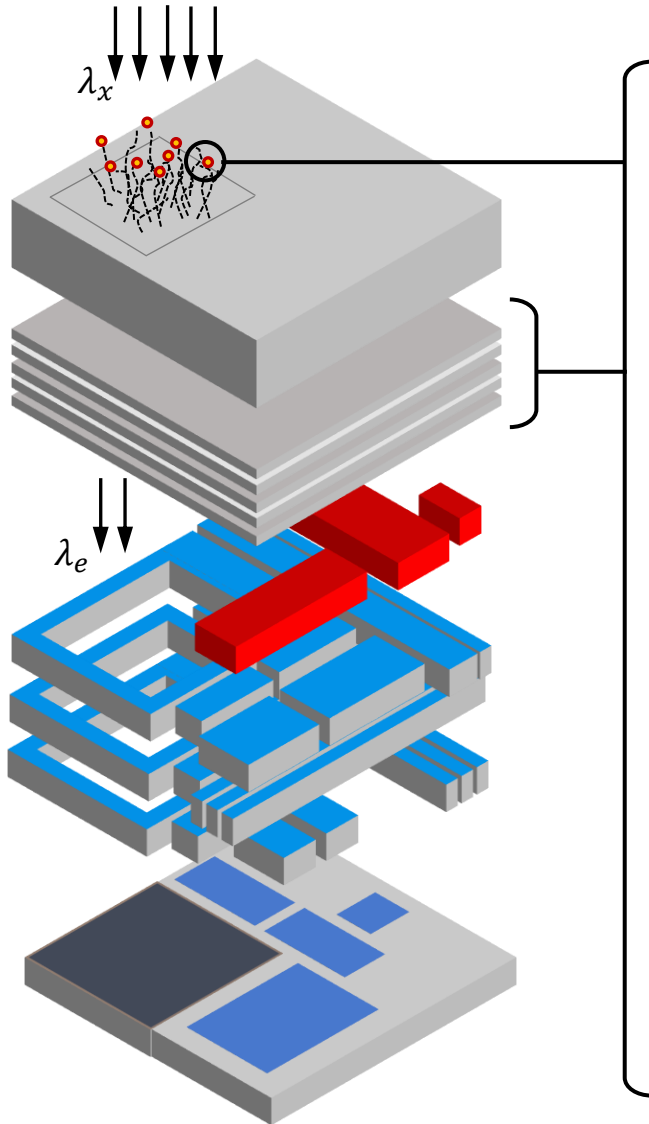


BIOSENSOR  
"PIXEL"

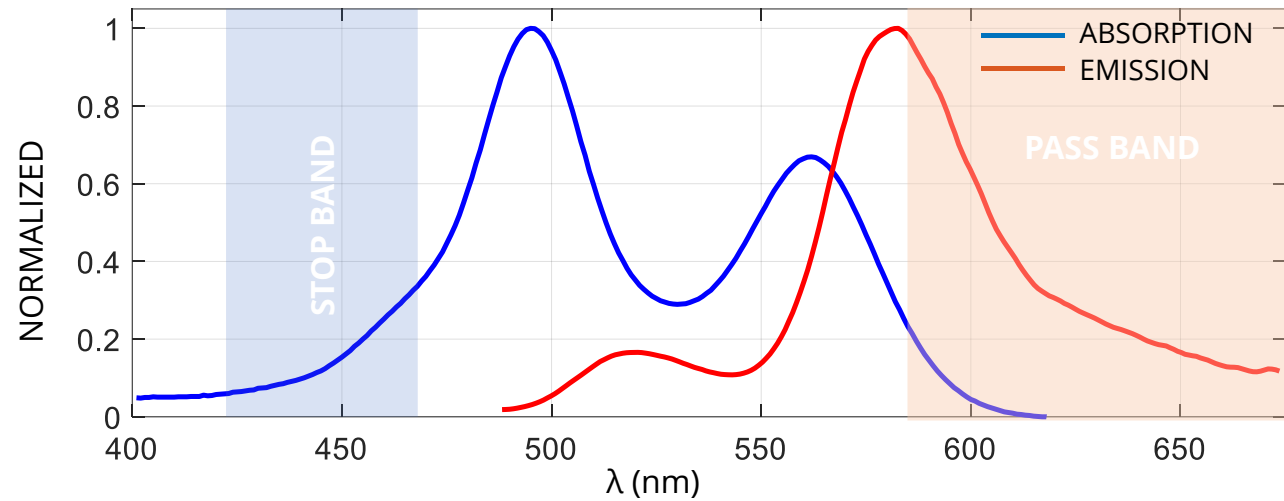


# Integrated emission filter

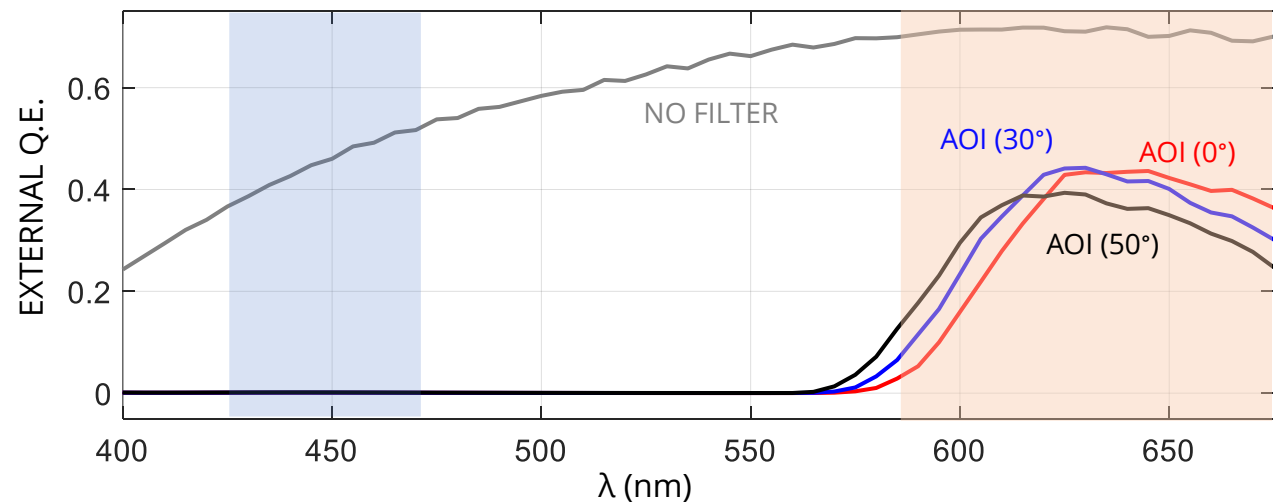
An angle-insensitive interference emission filter with  $10^6$  blocking in its stop-band



### FLUOROPHORE SPECTRA

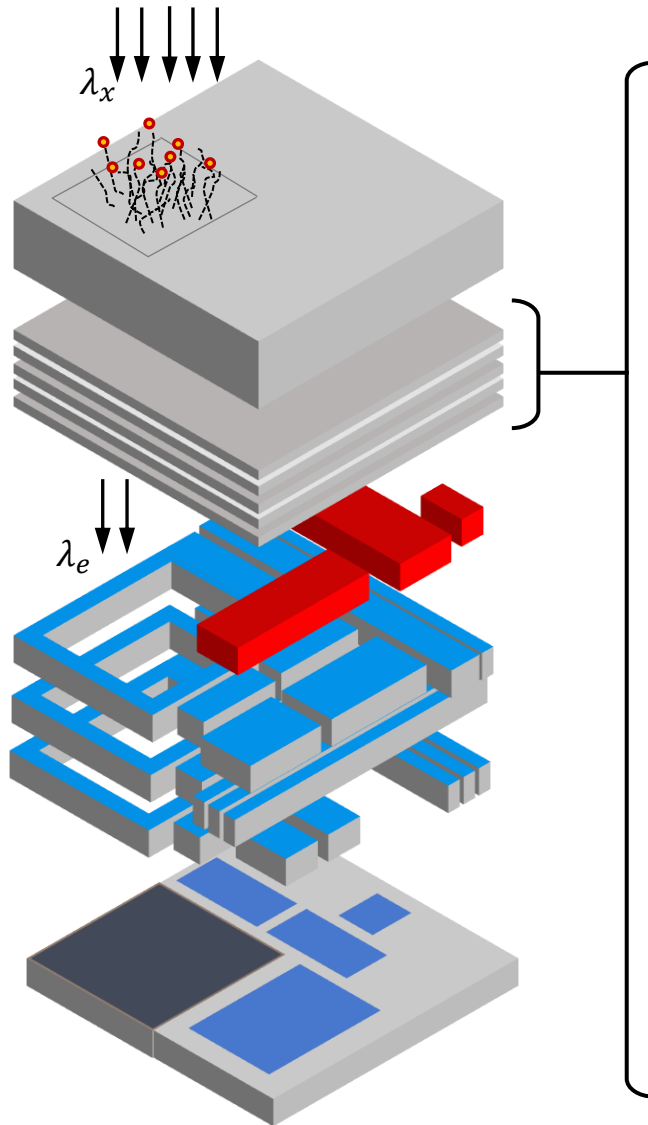


### BIOCHIP RESPONSE

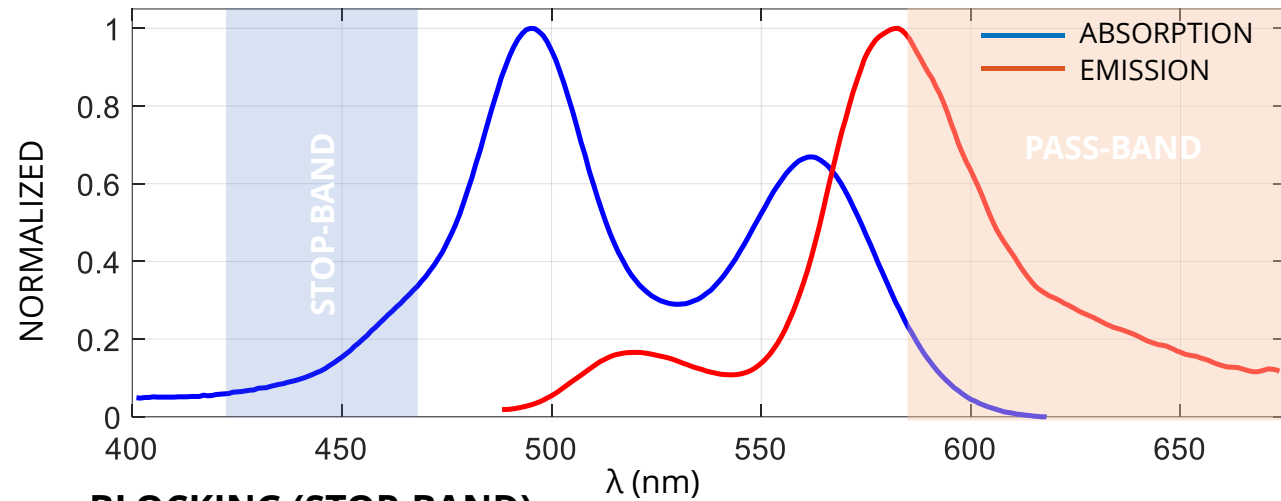


# Integrated emission filter

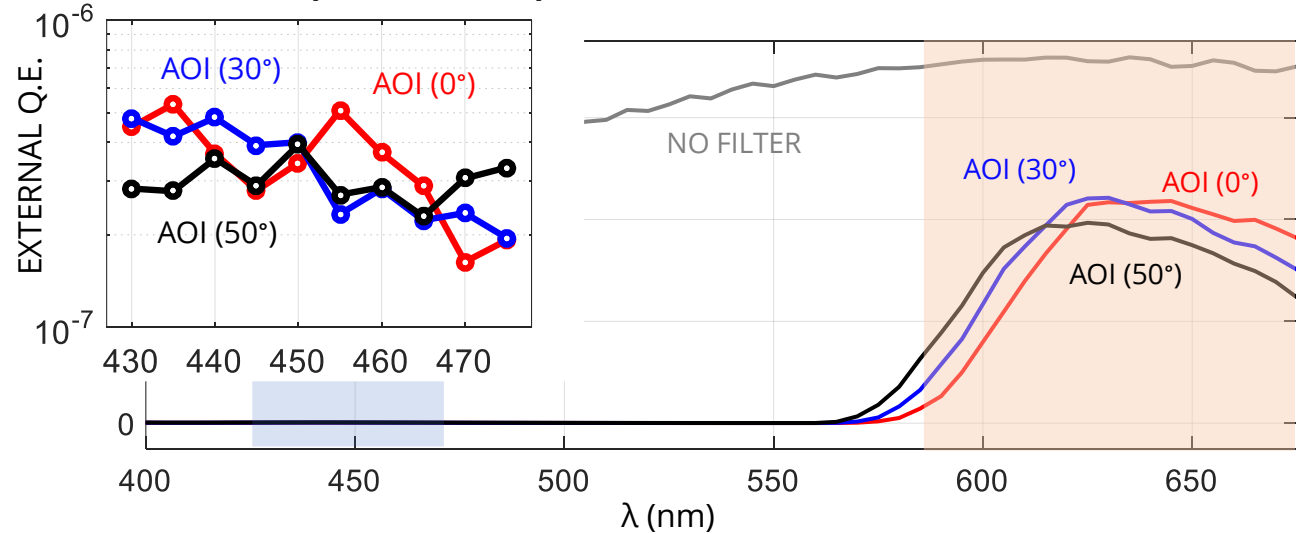
An angle-insensitive interference emission filter with  $10^6$  blocking in its stop-band



### FLUOROPHORE SPECTRA

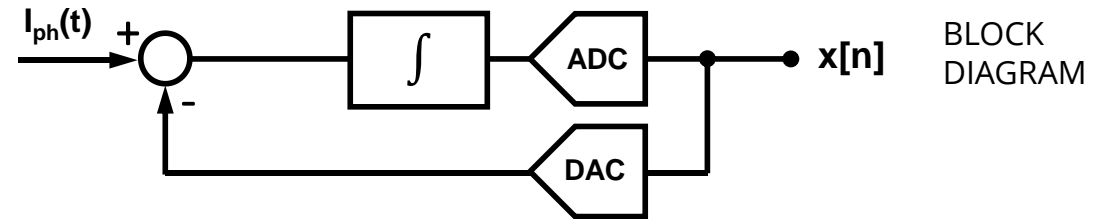
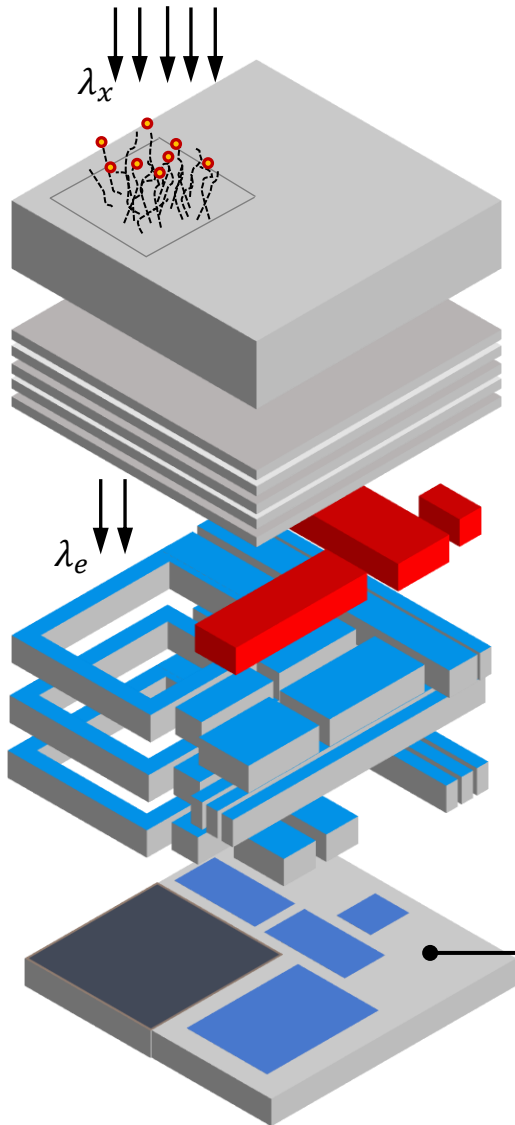


### BLOCKING (STOP-BAND)



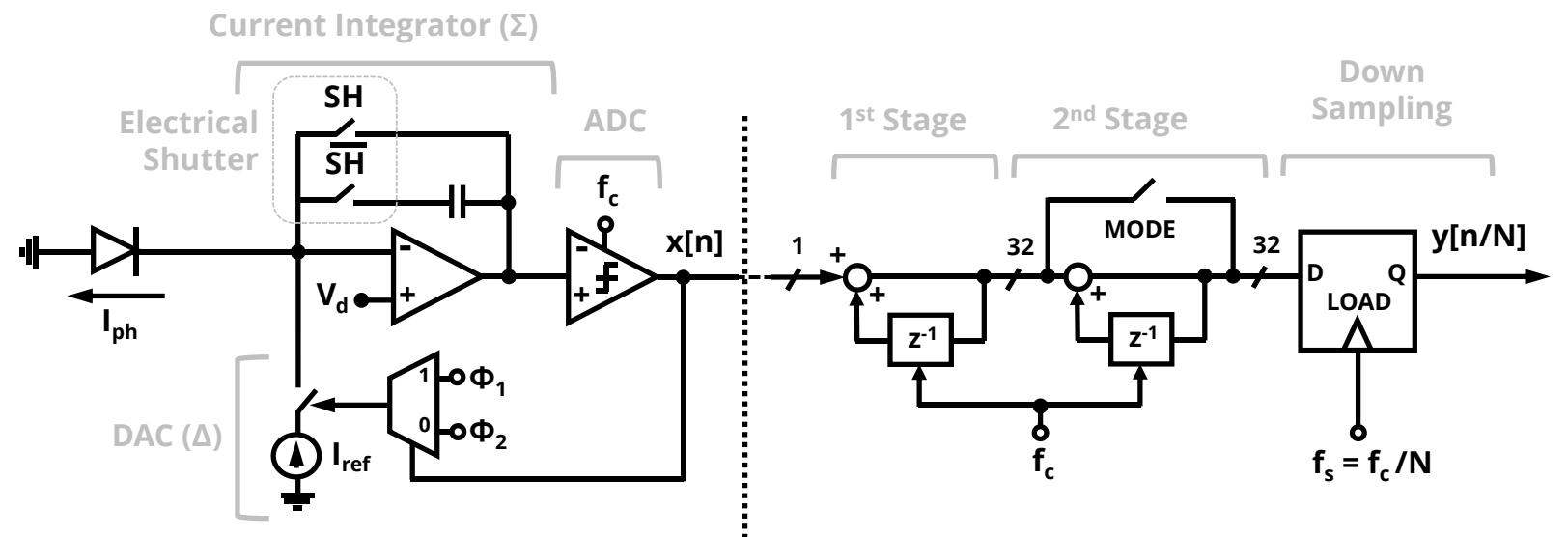
# In-pixel photosensor architecture

Photocurrent ( $I_{ph}$ ) detection using an in-pixel 1<sup>st</sup>-order  $\Sigma\Delta$  current sensor

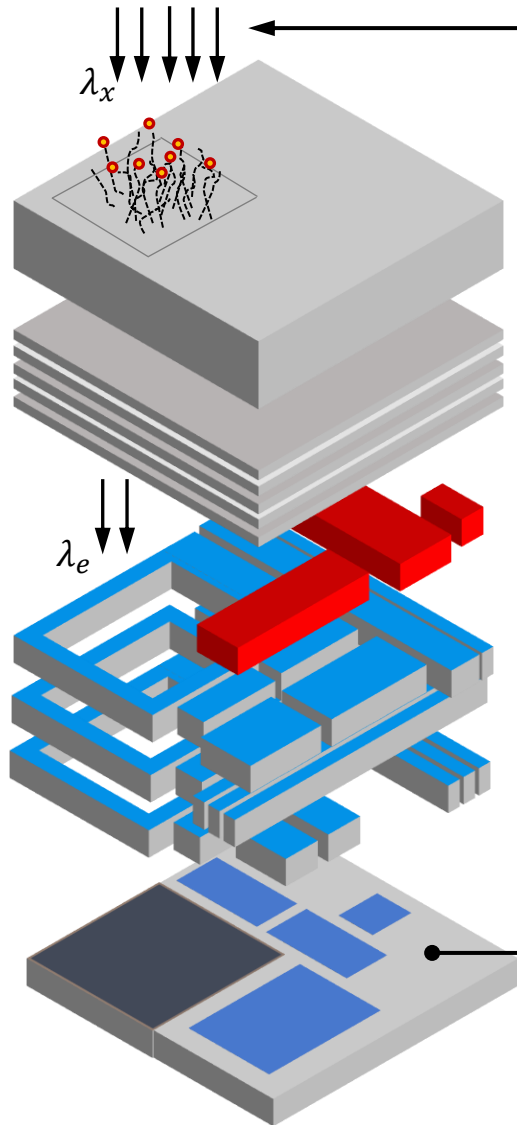


IN-PIXEL TOPOLOGY

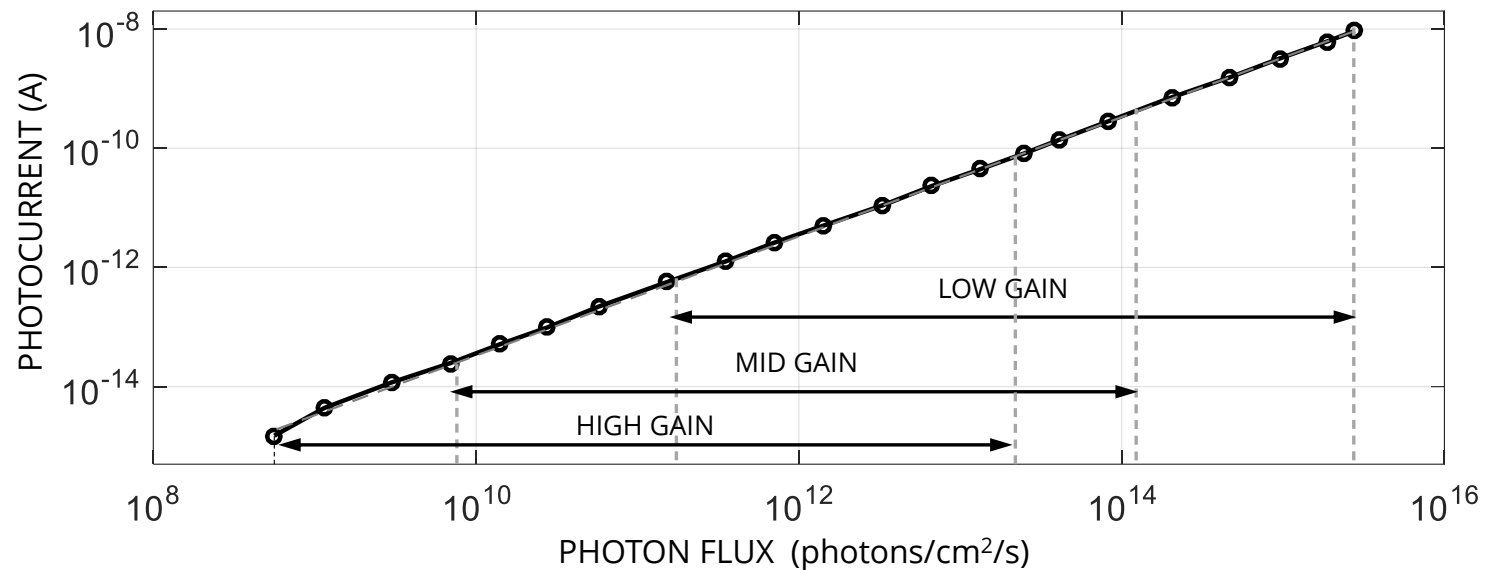
OFF-PIXEL DECIMATION BIT-CELL



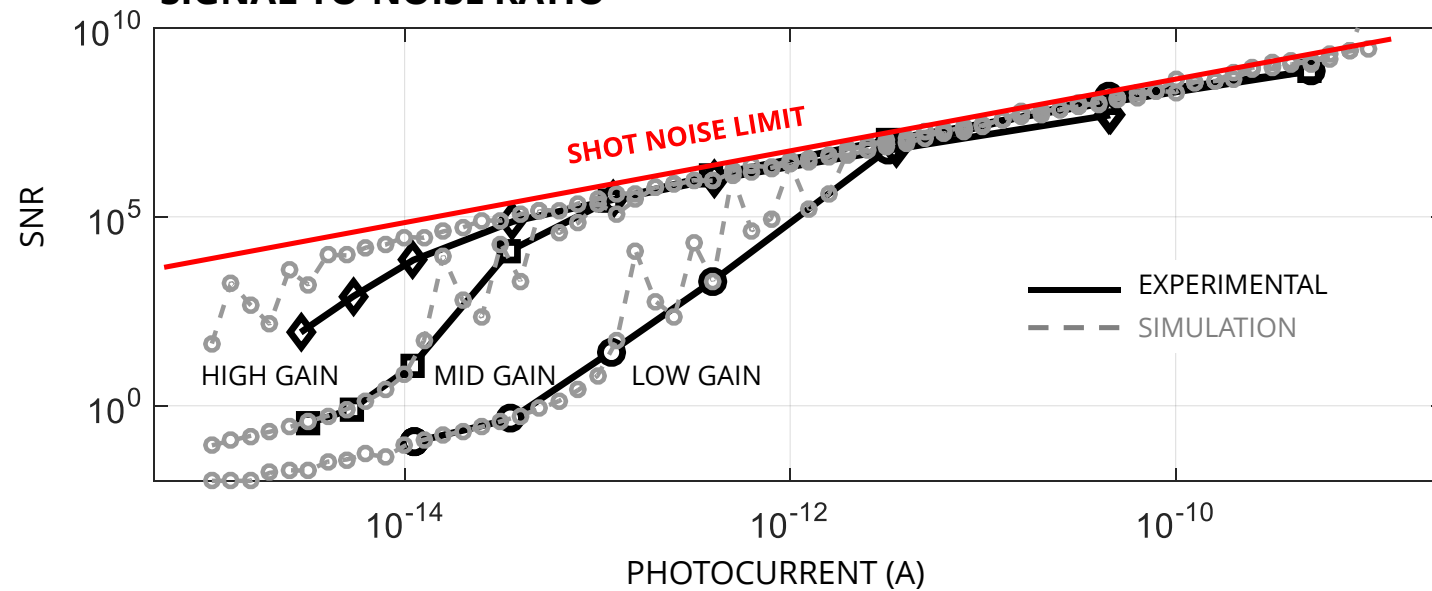
# Performance



## DETECTION DYNAMIC RANGE

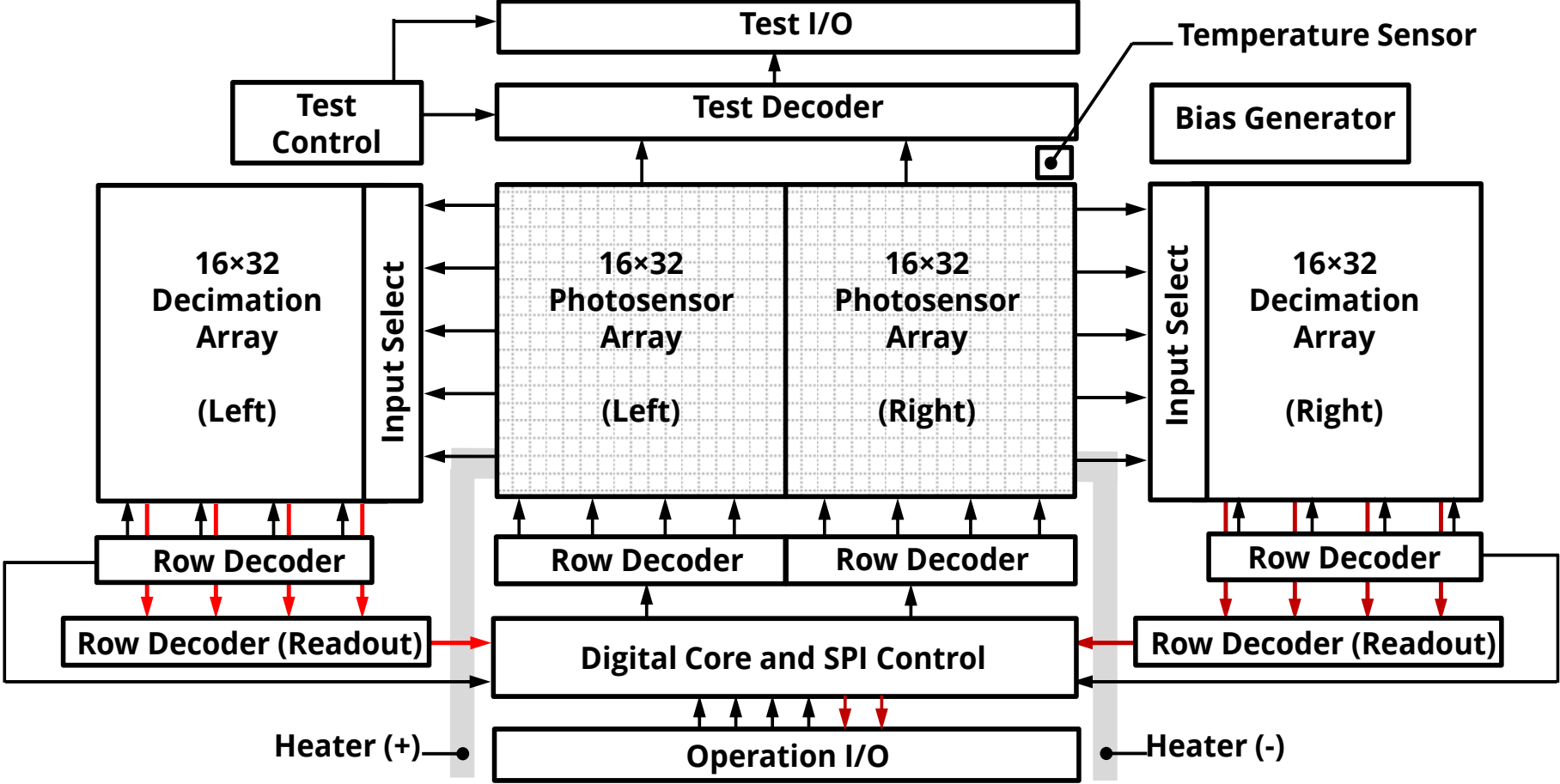
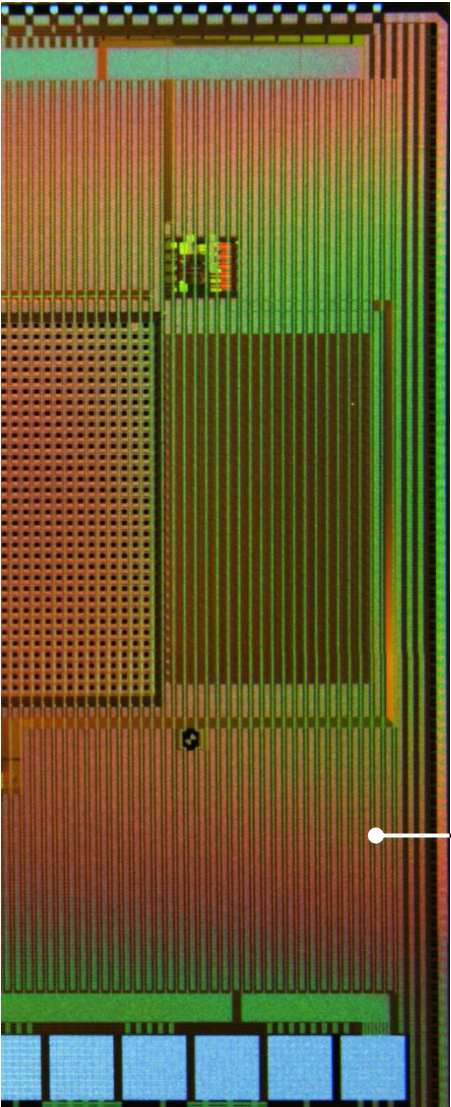


## SIGNAL-TO-NOISE RATIO

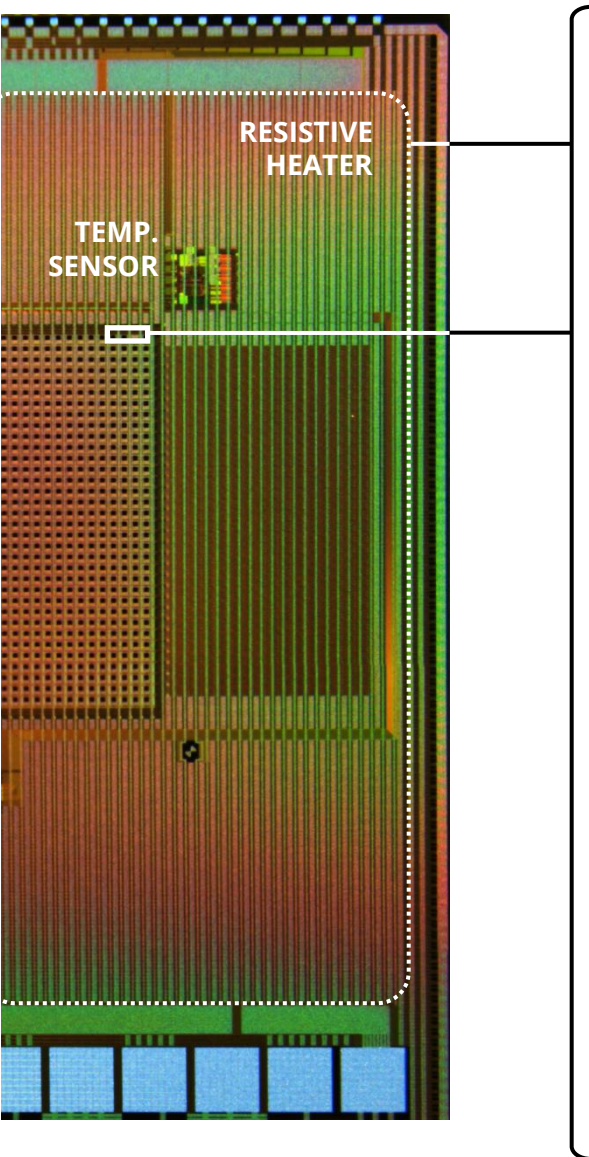




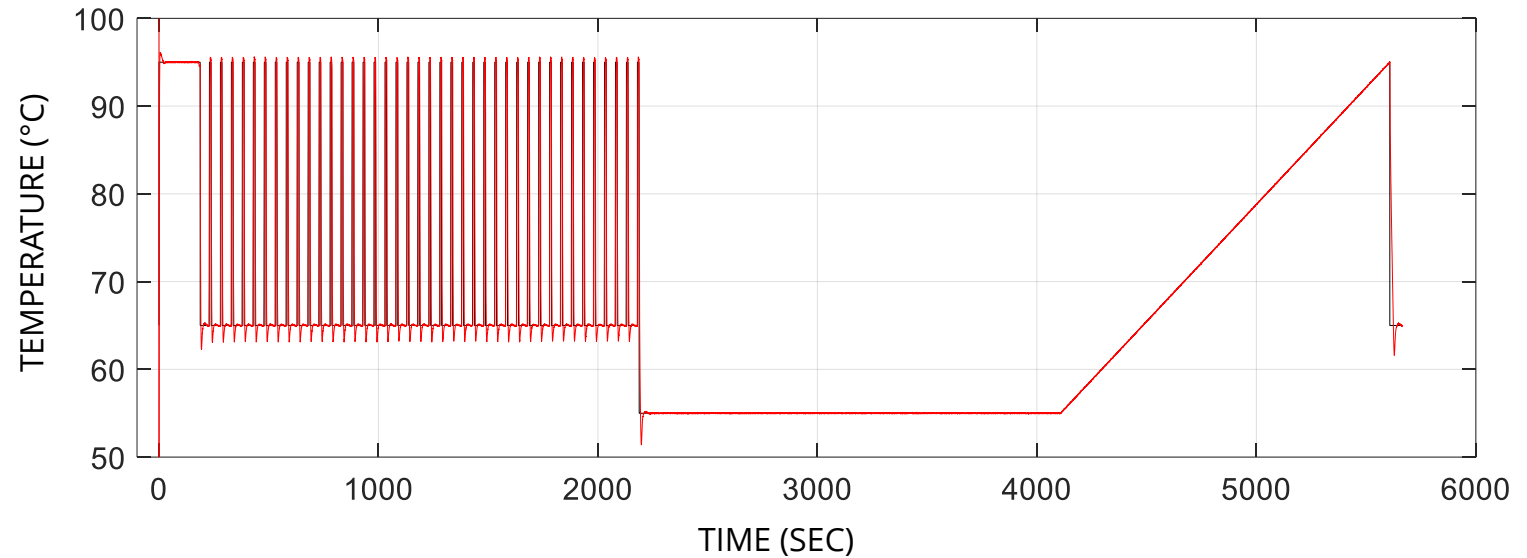
# Biochip Architecture



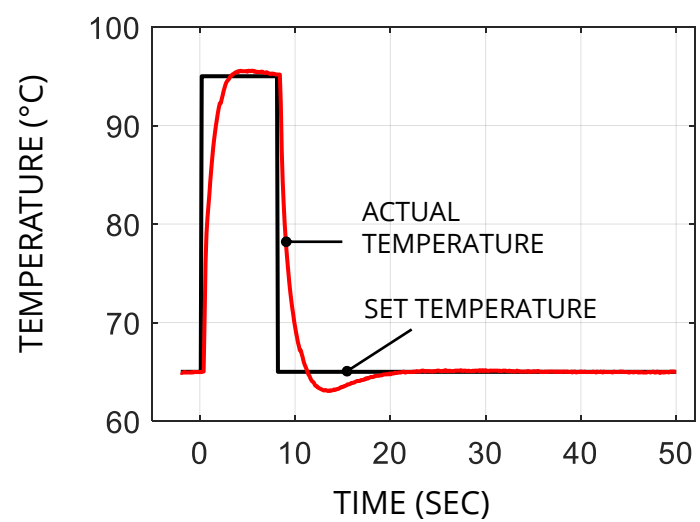
# Thermal performance for PCR



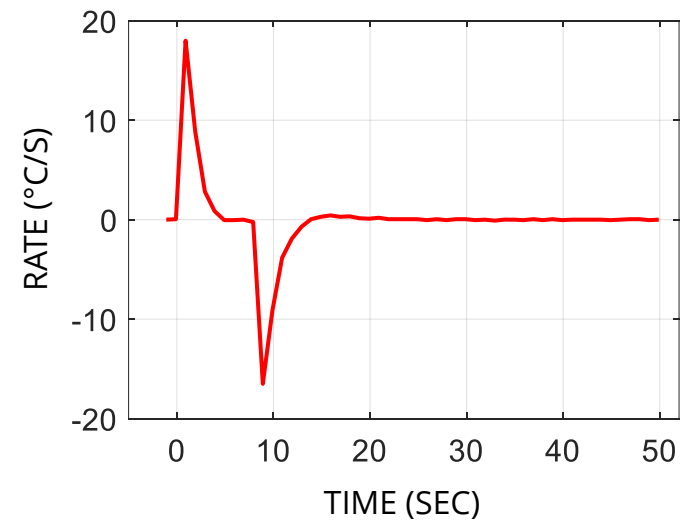
### PCR PROFILE + MELT (TYPICAL)



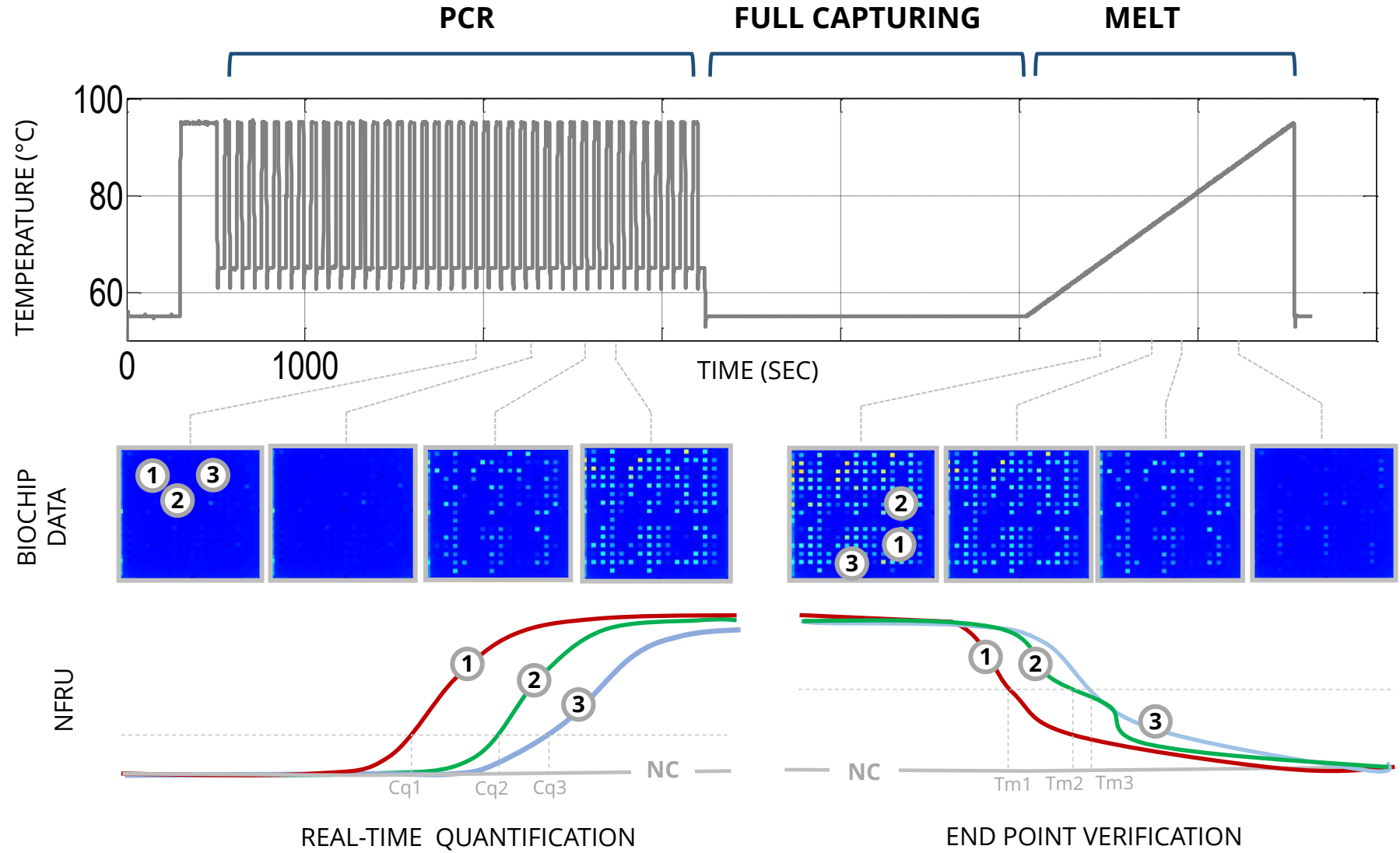
### PCR CYCLE



### HEATING + COOLING RATE

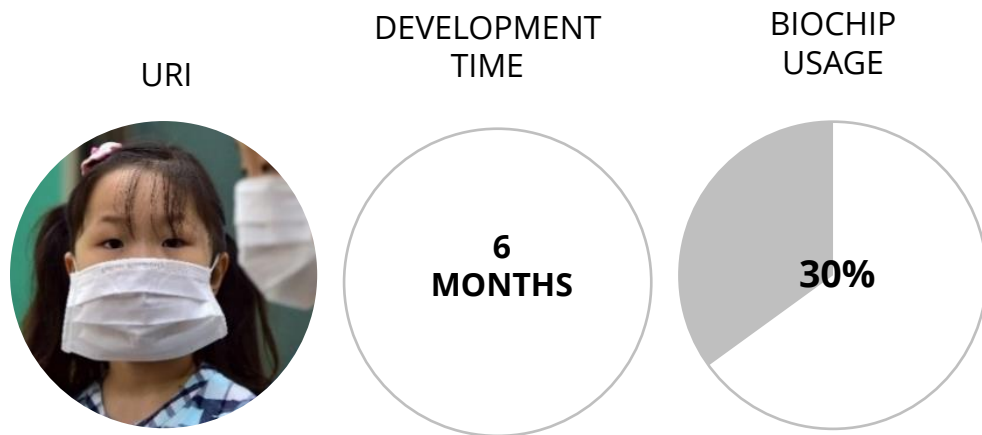


# Typical MDx workflow



# Upper respiratory infection (URI) CMOS biochip

**TEST:** Comprehensive detection of 28 bacteria and viruses relevant to URI's

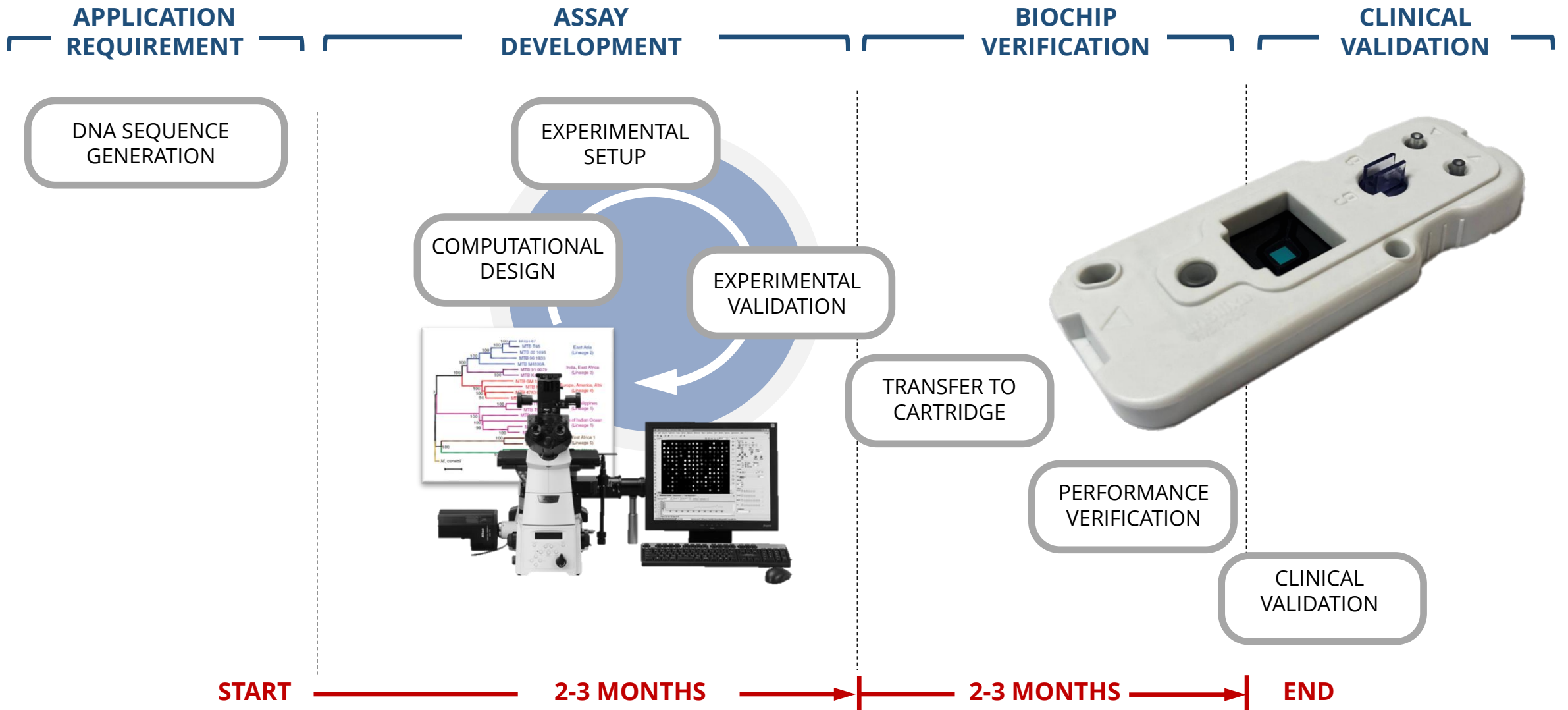


**DATABASE:** Internal  
**TARGETS:** 28  
**PROBES:** 80 (Redundancy = 4)

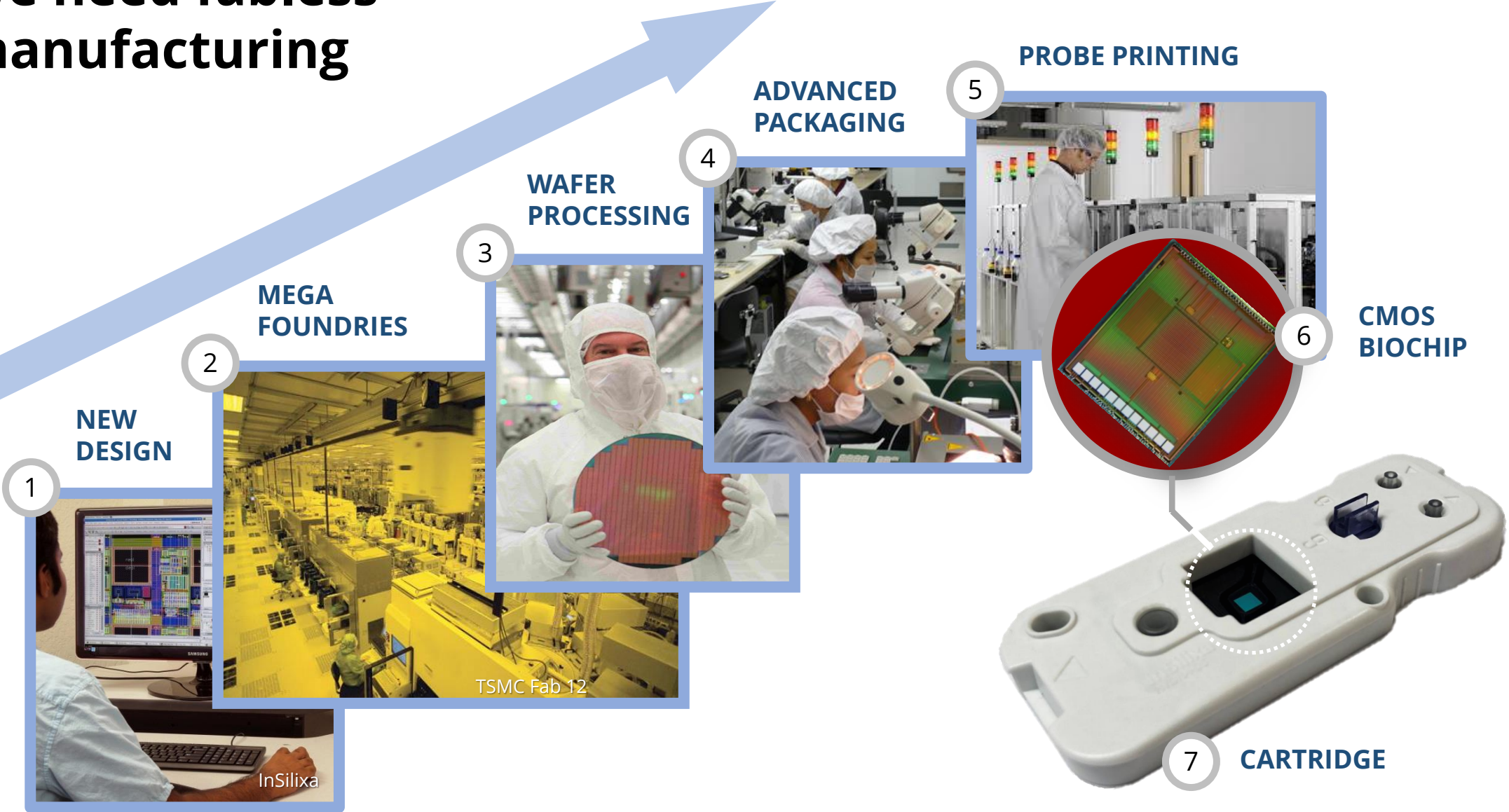
Panel Number	Organism Name	Target Type	Inclusivity Strains
1	Pan Flu A (Segments 7 and 8)	(-)RNA virus	8956 (segment 7)
2			7954 (segment 8)
3	H1 Flu (Segment 4)	(-)RNA virus	10,797
4	H3 Flu (Segment 4)	(-)RNA virus	12,489
5	Pandemic 2009 H1N1 (Segment 6)	(-)RNA virus	5533
6	Flu Antiviral Resistance (H275Y)	(-)RNA virus (SNPs)	5533
7			3371 (segment 7)
8	Pan Flu B (Segments 7 and 8)	(-)RNA virus	4576 (segment 8)
9	Pan RSV	(-)RNA virus	787
10	Parainfluenza 1	(-)RNA virus	18
11	Parainfluenza 2	(-)RNA virus	6
12	Parainfluenza 3	(-)RNA virus	79
13	Parainfluenza 4	(-)RNA virus	8
14	Pan Human Metapneumovirus	(-)RNA virus	121
15	Adenovirus B	DNA virus	127
16	Adenovirus C	DNA virus	28
17	Adenovirus E	DNA virus	8
18	Coronavirus 229E	(+)RNA virus	7
19	Coronavirus NL63	(+)RNA virus	63
20	Coronavirus HKU1	(+)RNA virus	31
21	Coronavirus OC43	(+)RNA virus	91
22	SARS-CoV-2	(+)RNA virus	15,900
23	Human Enterovirus D68	(+)RNA virus	95
24	Enterovirus/Rhinovirus (Combined)	(+)RNA virus (Variant Region)	657
26	<i>M. pneumoniae</i> (P1)	bacterium	40
27	<i>C. pneumoniae</i> (ompA)	bacterium	80
28	<i>B. pertussis</i> (ptxA)	bacterium	1041
29	Human RPL32 (Sample Control)	host (human) DNA	3
30	S.Pombe (Process Control)	yeast	1

Looking forward ...

# We need rapid application development



# We need fabless manufacturing



# We need “more evolved” behavior

Prevention? Diagnostics? Invest time/money?

How about now?



Nope, I am good.



**IT HURTS!**

Where is my treatment?

Where is my vaccine?

Kill all the pangolins!

Invest in fried bananas!

Masks suck!



# Mass-deployable Molecular Diagnostics (MDx), including COVID-19 Testing: An IC Designer's Perspective

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