A Novel Genetic Algorithm for Detecting FLT3 Internal Tandem Duplications in Acute Myeloid Leukemia Patients

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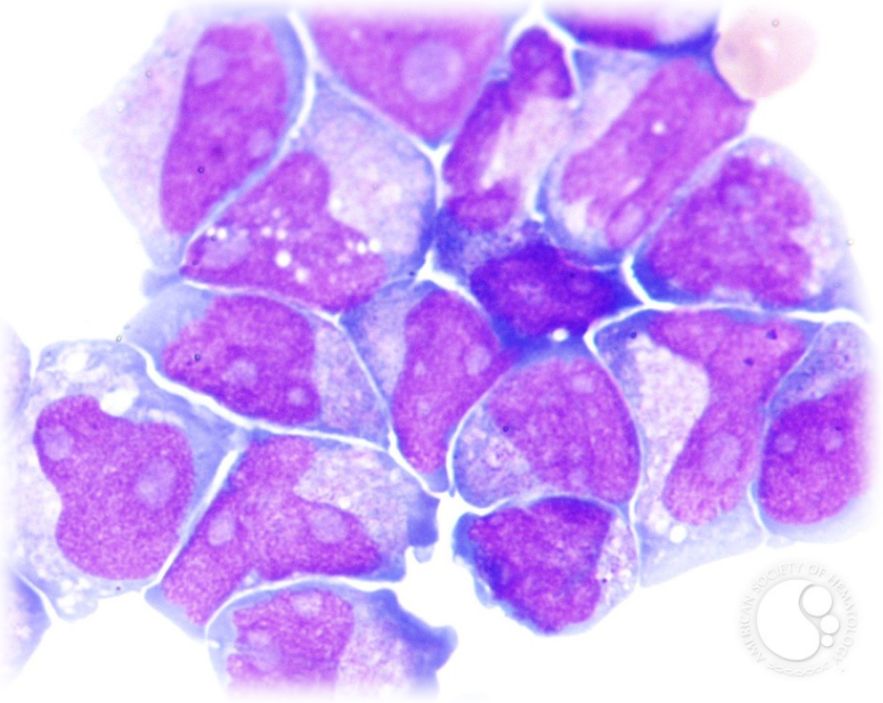
Background



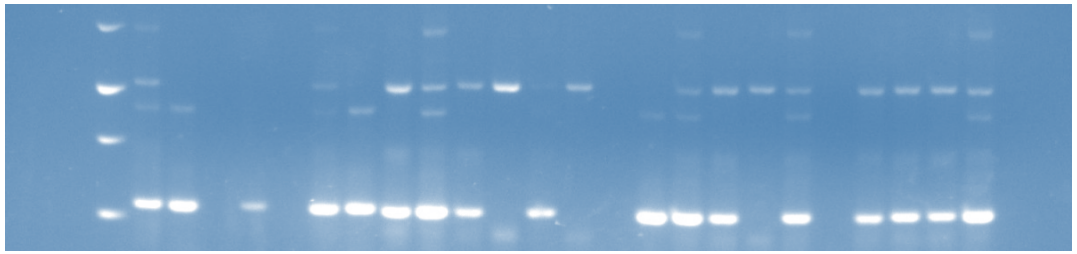
- Treating Acute Myeloid Leukemia
  - 20,000 expected cases in 2016
- Target: “Unfavorable” FLT3-ITD^{+} subtype
  - ITD = Internal Tandem Duplication*
- **Goal:** Identify ITD^{+} individuals for future clinical trials

*

Identifying ITD^{+} Drug Candidates

PCR

- Lacks potentially useful info:
  - Sequence
  - Precise location, length
- Inaccessible



Next Generation Sequencing

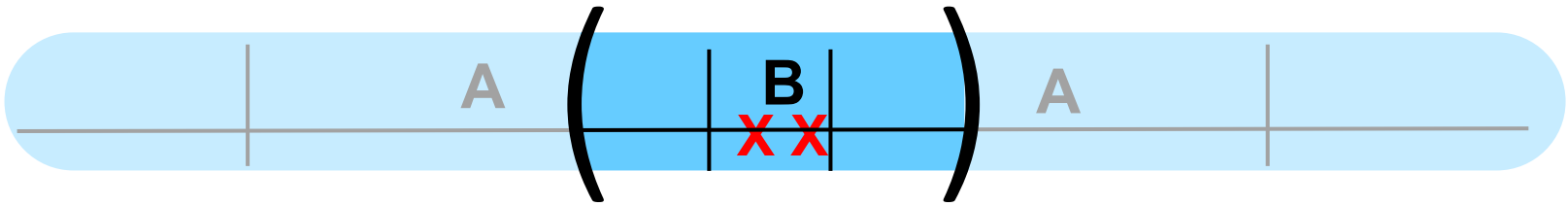
- Best at finding small variants:
  - SNPs
  - Short insertions & deletions
- Limited software for ITDs

```
ACTGTACCAGGACGCGCGCAGGGGGGAGGGGTACCTTCGGTCGACA
ACACCAGGTGGAGCGGGGGCAATCTTACGCTGCGGGGCAACTCCCC
TGTGTATAGTAGTATAGCGGCTAATGATCTACGGTTTACGTTATAA
AGGGAGCAGCGTTCGCTTATTGGAAGTAGTATAGGTTCGGCGATAT
CTCCGCGATAGGAGCAGTATCGAGGGTCACTGAACGTTCAGGGGGC
```

Challenges to ITD Discovery

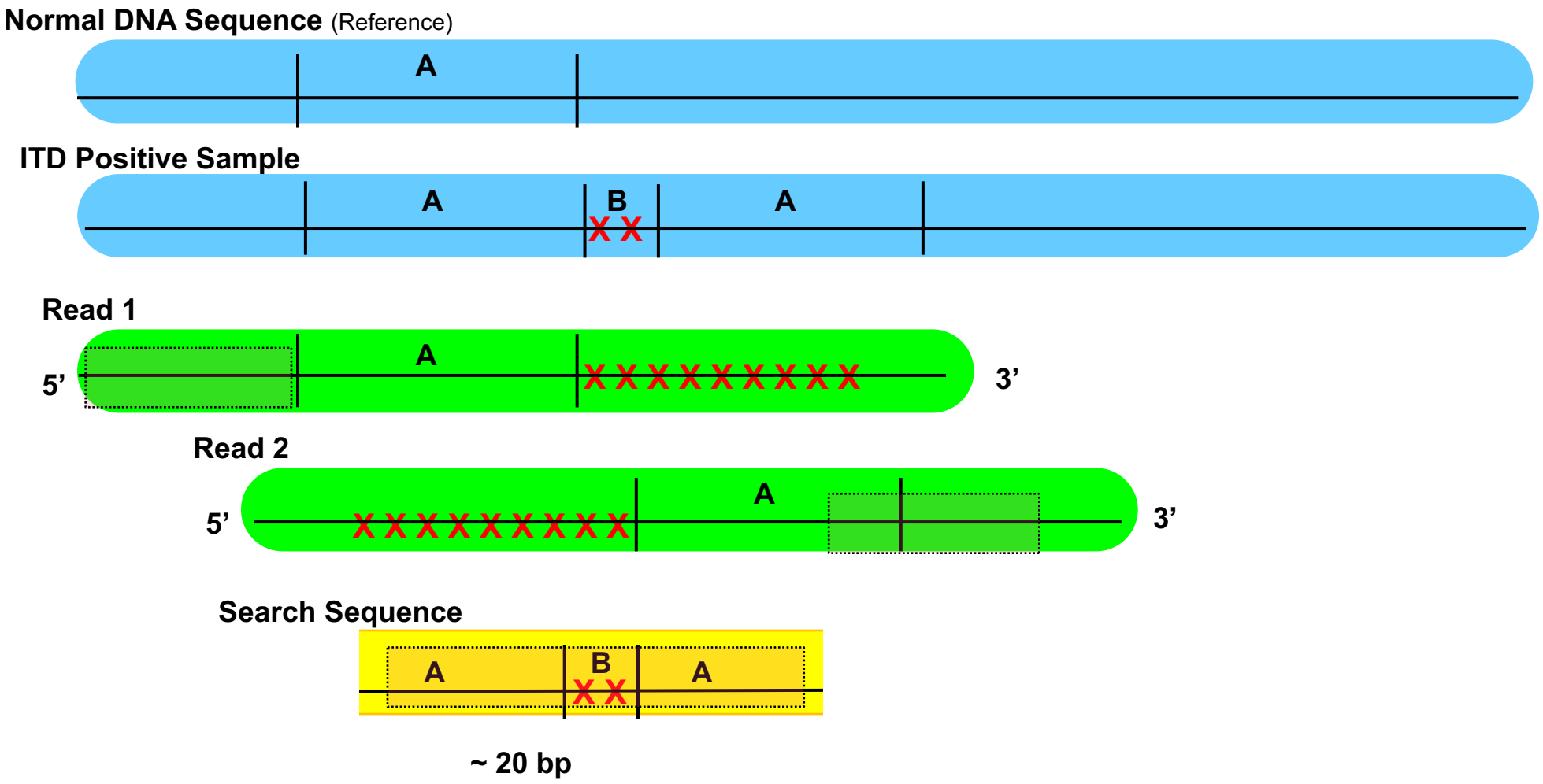
- Vary in location, length, and frequency!

Claim: The ~ 20bp "Junction of Duplication" uniquely identifies FLT3-ITDs.

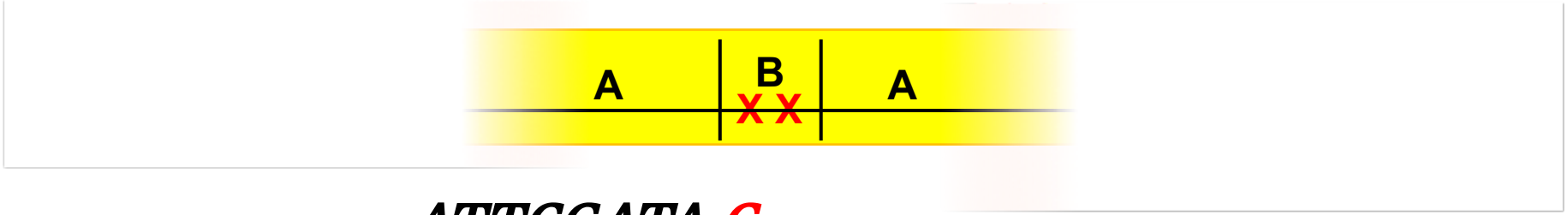


Probability of same sequence occurring by random chance in the region of interest is: $\frac{1}{4^{20}} \times 10^3 \approx \frac{1}{10^9}$

An Algorithm for Detecting ITDs in FLT3



Flexible Searching with Regular Expressions



$$ATTCGATA\ C\ldots$$

$$\ldots A\ CGAAGTTC$$

$$ATTCGATA\ (\ C\ \ [ACTG]\{0,m\}\ \ A\ )\ CGAAGTTC$$

Left Probe $[0:n-1]$ *LP* $[n]$ *between 0 and* m *bases* *RP* $[0]$ *Right Probe* $[1:n]$

Example parameters:

$$n = 13$$

$$m = 30$$

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FLT3 ITD Identification Results

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`9996_S7` is **ITD positive**, with `168` supporting reads and `2` possible duplications.

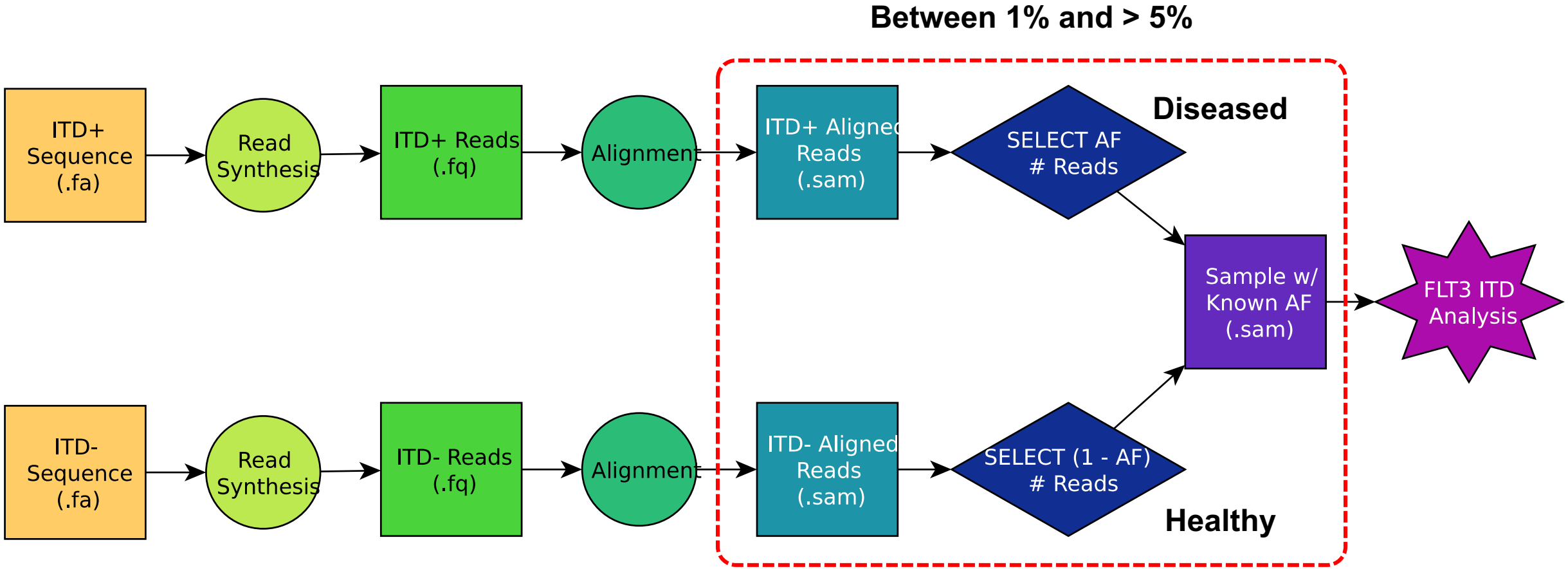
Duplication 1

Location	Length	Reads	Non-ITD Reads	Allele Frequency	Reads with entire ITD
28608262	51	118	769	0.13303	80

Sequence:

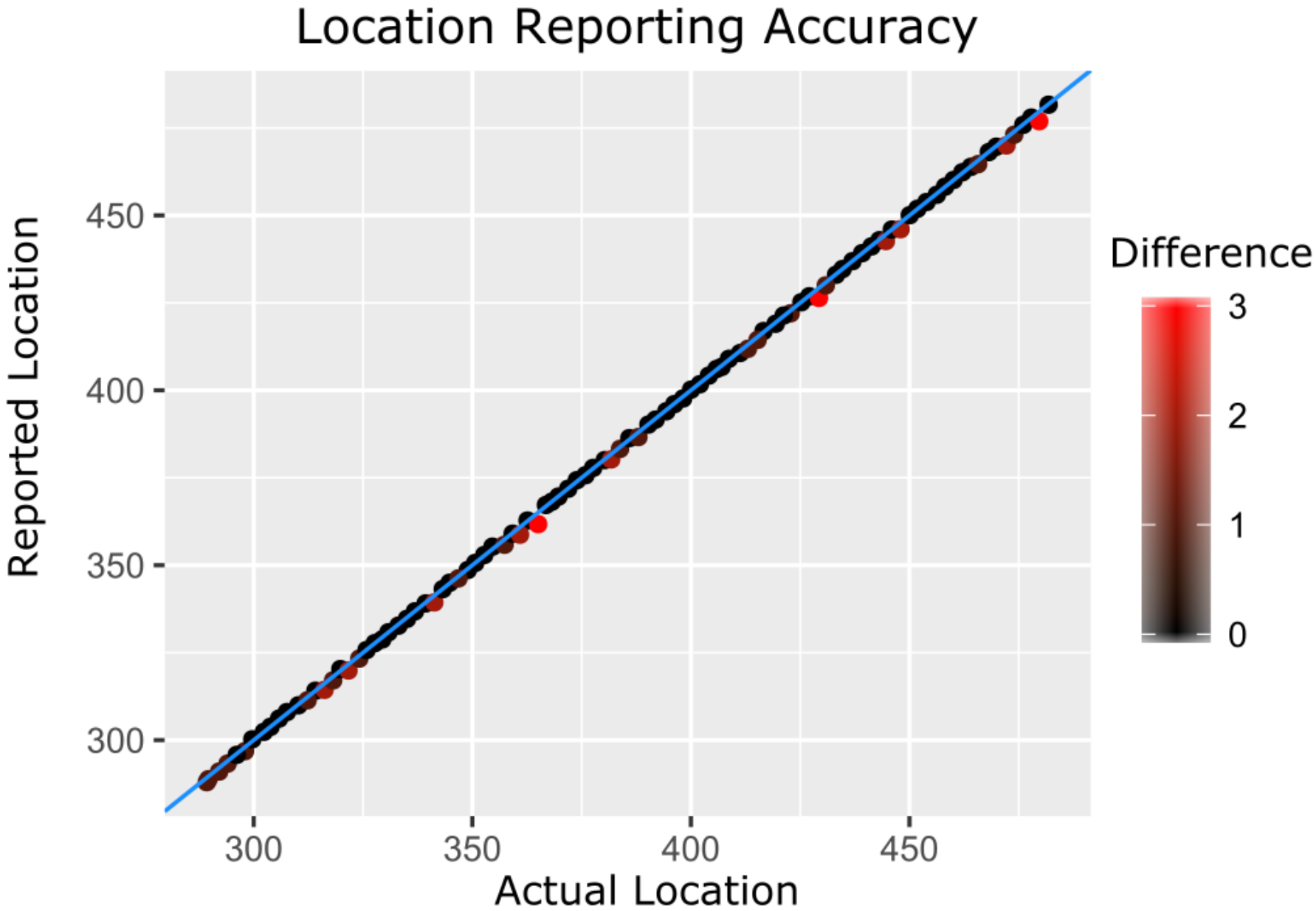
```
ATATGATCTCAAATGGGAGTTTCCAAGAGAAAATTTAGAGTTTGGattccc
```

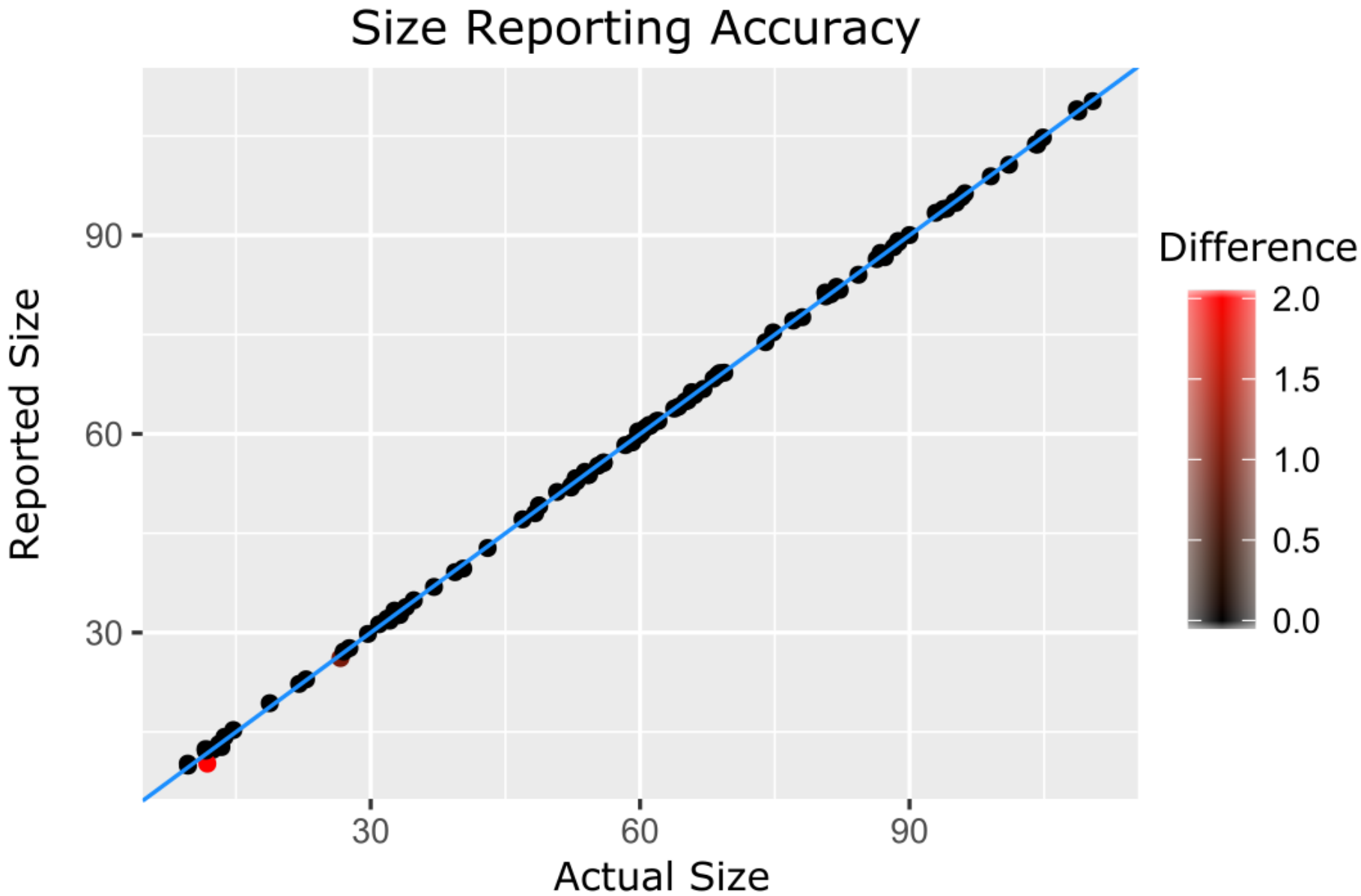
in silico Testing Procedure



Specificity:
99.9%

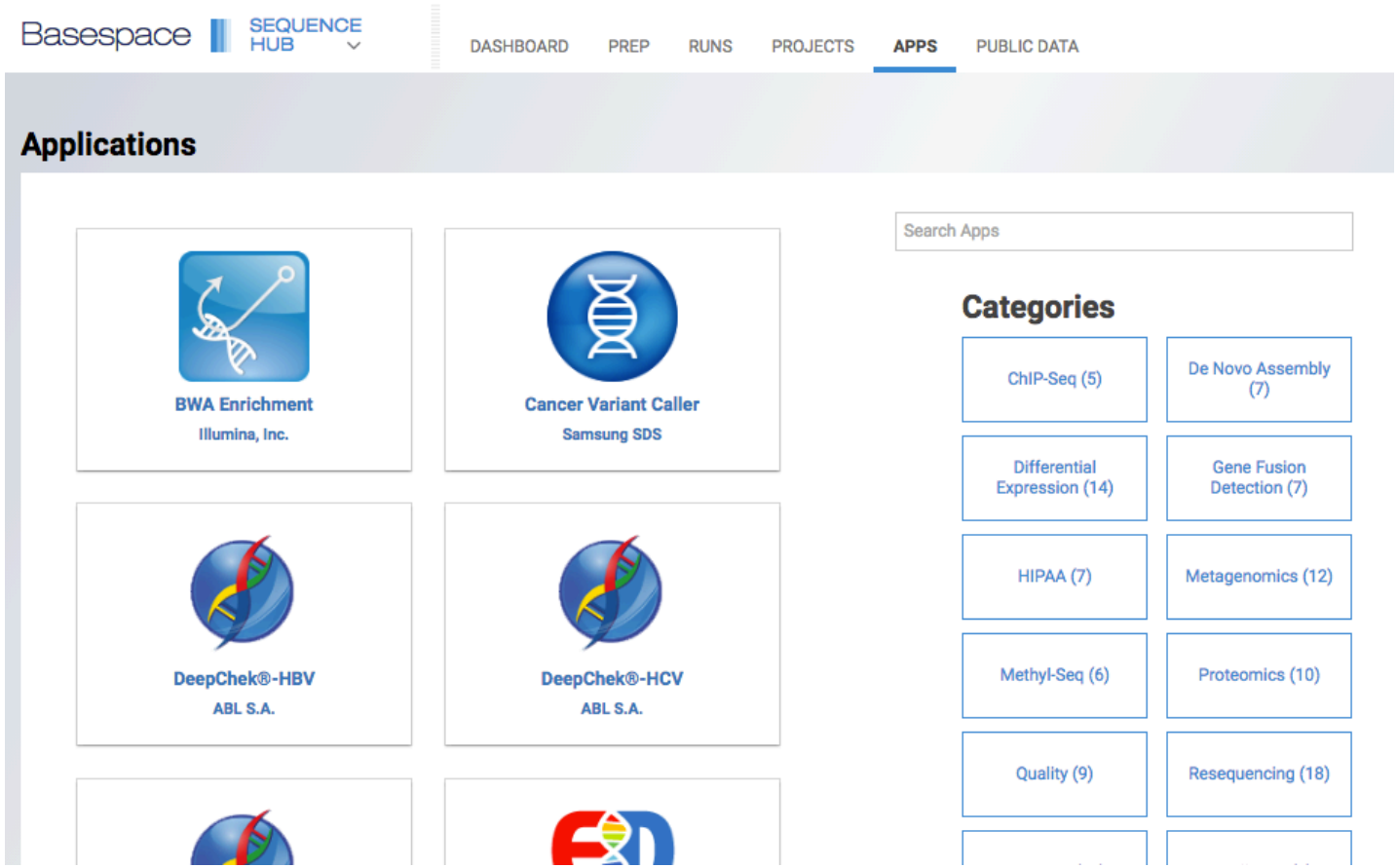
Sensitivity:
(assuming AB > 2%)
100%


Location Reporting Accuracy
Reported Location
450
400
350
300
300
350
400
450
Actual Location
Difference
3
2
1
0


Size Reporting Accuracy
Reported Size
90
60
30
30
60
90
Actual Size
Difference
2.0
1.5
1.0
0.5
0.0

Using the Algorithm Offsite

BaseSpace®



Thank you!

Plexxikon

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NCCB

Berkeley EECS
ELECTRICAL ENGINEERING & COMPUTER SCIENCES

Friends and family!

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