Protecting Patient Privacy in Genomic Analysis

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Stanford University

based on joint works with:
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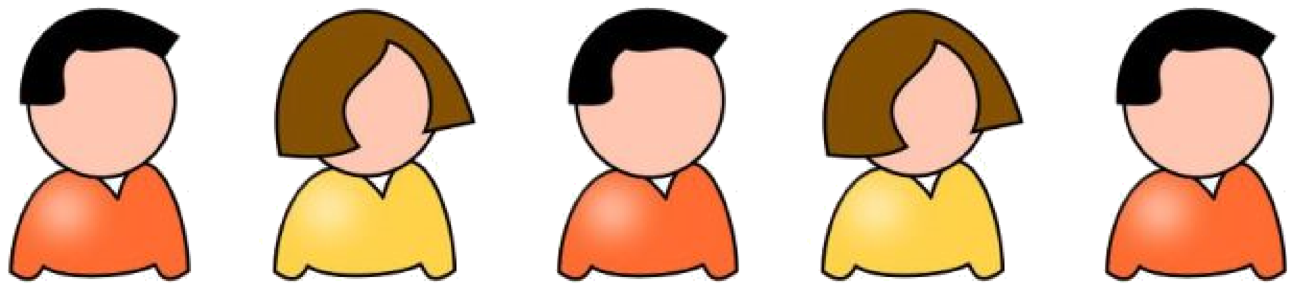
Dan Boneh, Hyunghoon Cho, and Karthik A. Jagadeesh

Rare Disease Diagnosis

Jagadeesh-W-Birgmeier-Boneh-Bejerano [Science 2017]

What gene causes a specific (rare) disease?



Patients with Kabuki Syndrome

Each patient has a list of 200-400 rare variants over ≈20,000 genes

Rare Disease Diagnosis

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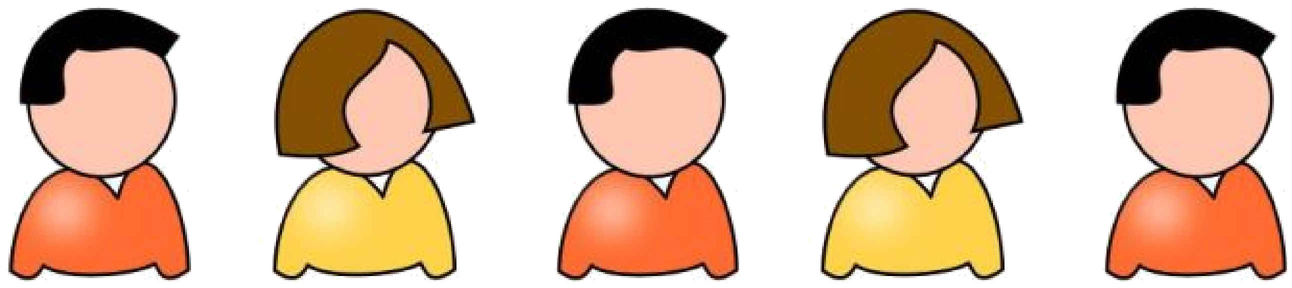
Gene					
A1BG	0	1	0	0	0
	1	1	1	0	1
	⋮	⋮	⋮	⋮	⋮
ZZZ3	0	0	1	0	0



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Each patient has a vector v where $v_i = 1$ if patient has a rare variant in gene i

Goal: Identify gene with most variants across all patients

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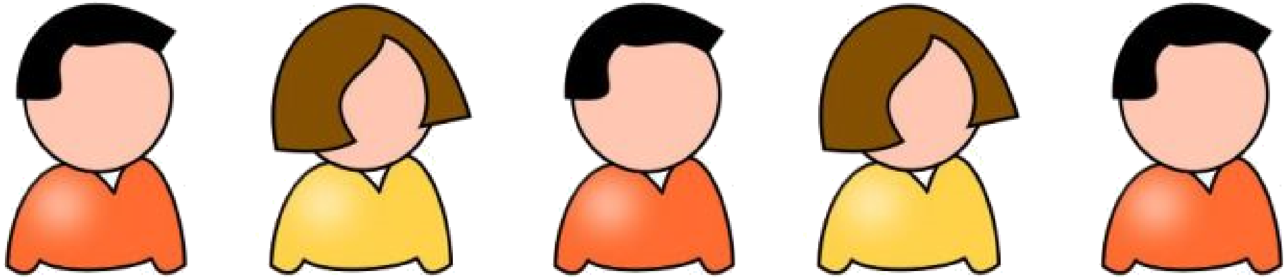

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Works well for <u>Mendelian</u> (monogenic) diseases (estimated to affect ≈10% of individuals)

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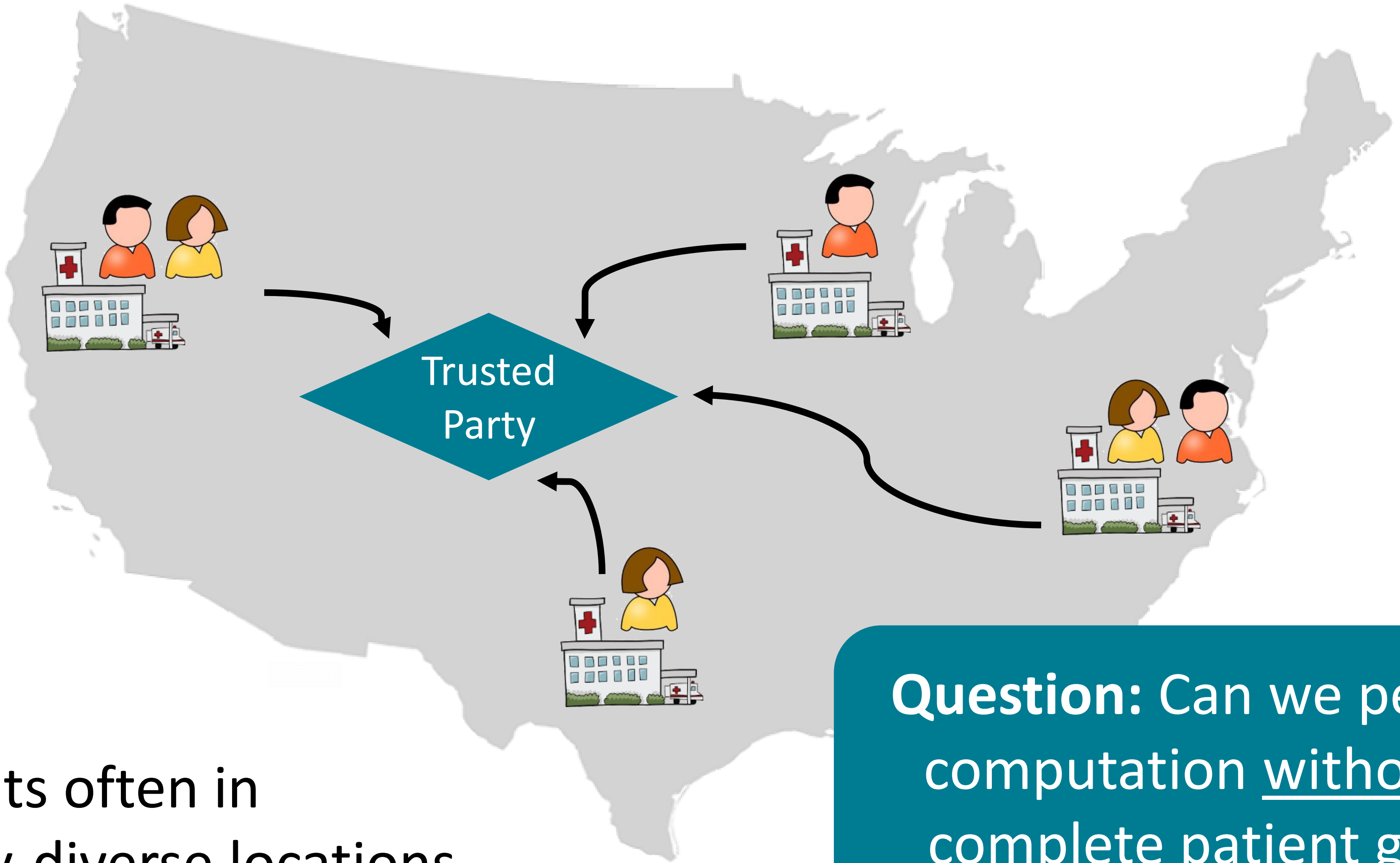

Patients often in geographically-diverse locations

Question: Can we perform this computation without seeing complete patient genomes?

Rare Disease Diagnosis

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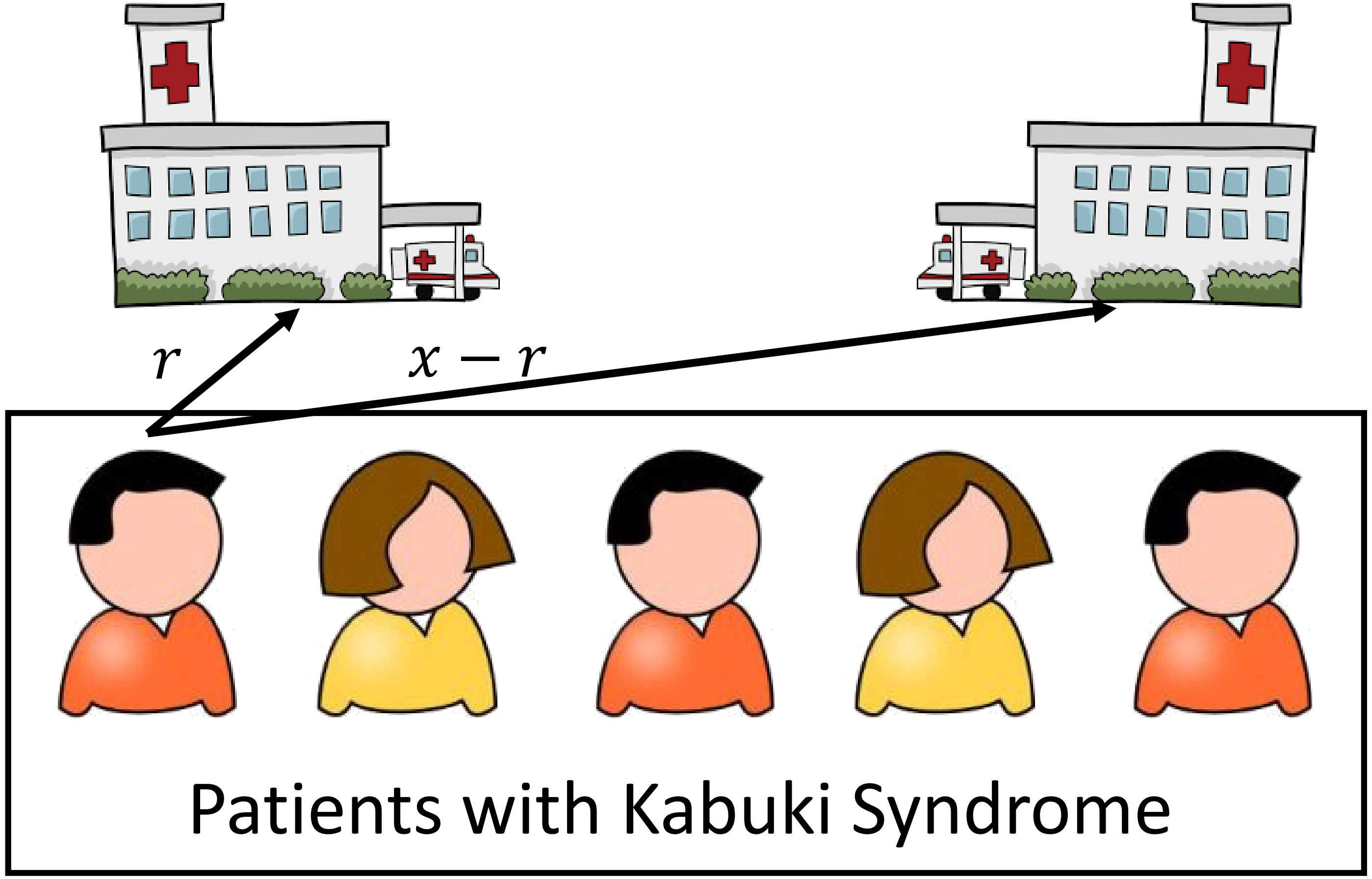

Patients "secret share" their data with two non-colluding hospitals

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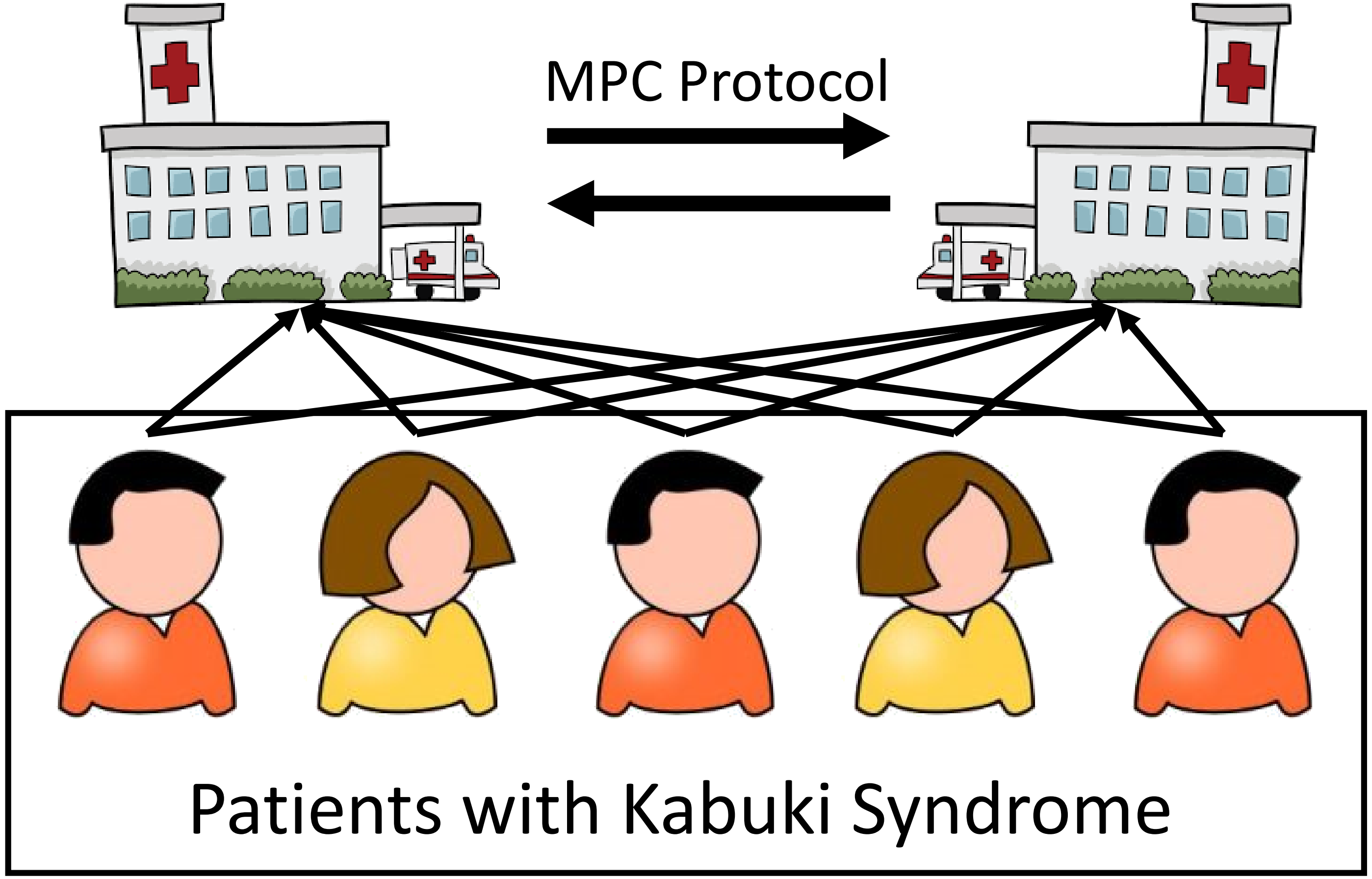

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Hospitals run a multiparty computation (MPC) protocol on pooled inputs

Patients "secret share" their data with two non-colluding hospitals

Rare Disease Diagnosis

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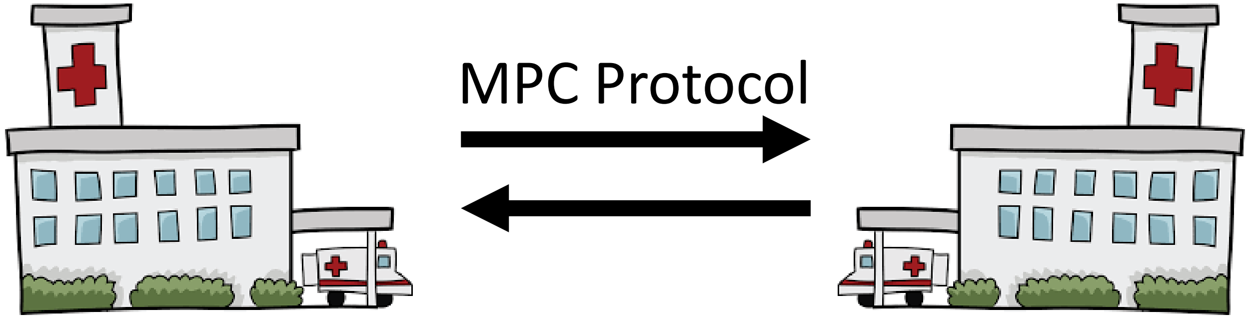

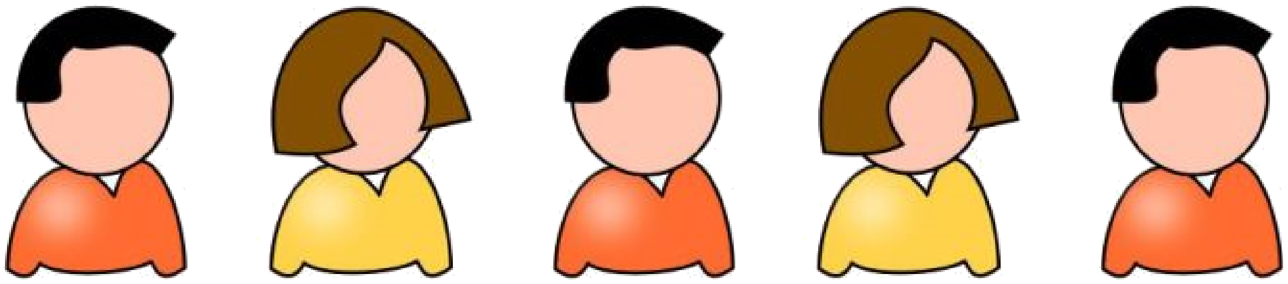

Patients with Kabuki Syndrome

Each patient has a list of 200-400 rare variants over ≈20,000 genes

Top variants (sorted):
KMT2D, COL6A1, FLNB

Known cause of disease

Rare Disease Diagnosis

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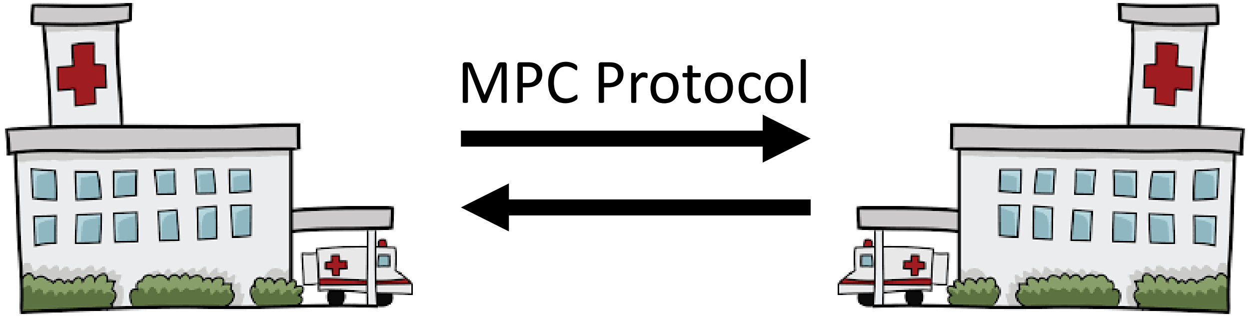

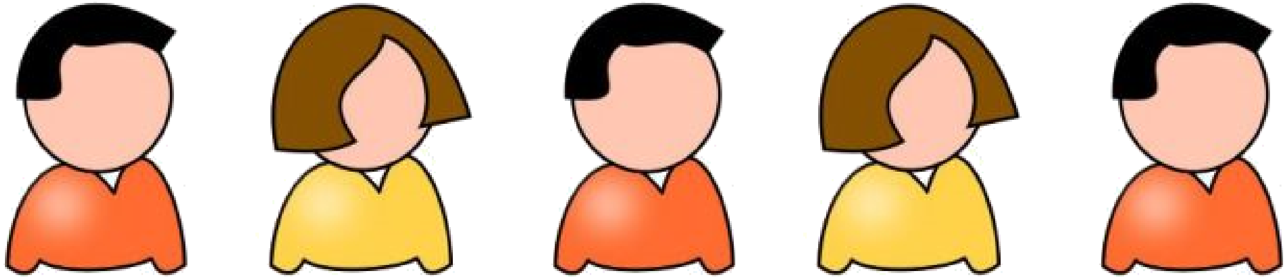

Patients with Kabuki Syndrome

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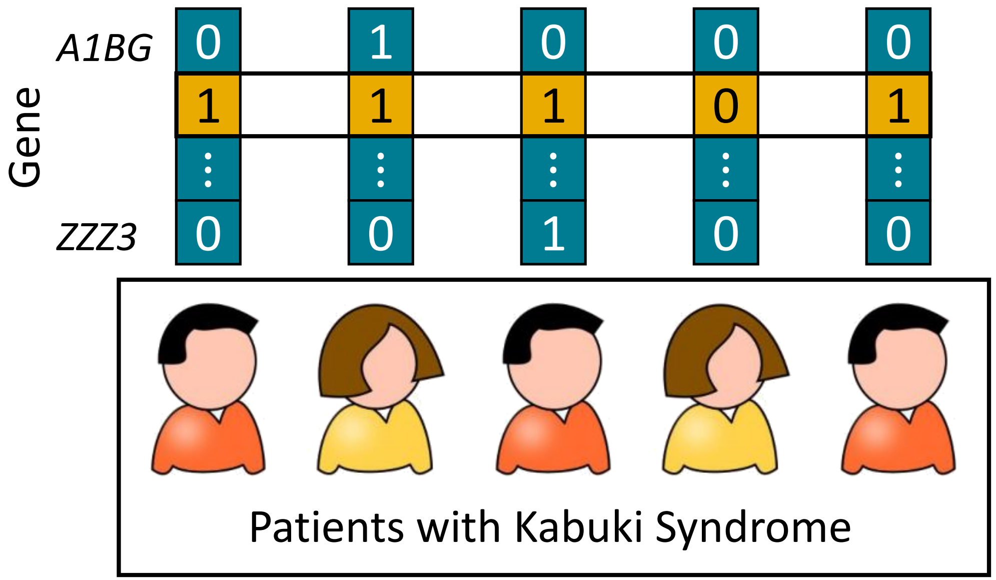
Other variants that the patients possess are kept <u>hidden</u>

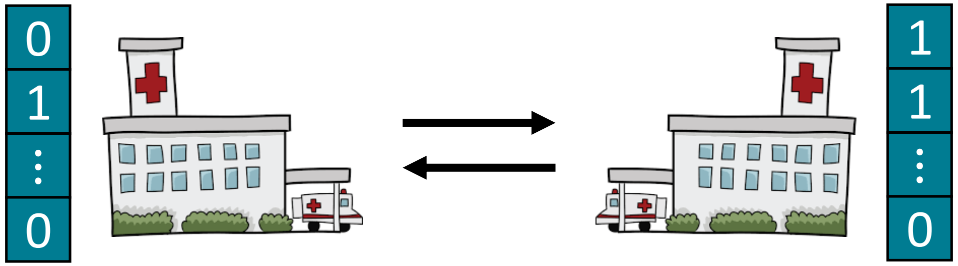
Rare Disease Diagnosis

Jagadeesh-W-Birgmeier-Boneh-Bejerano [Science 2017]

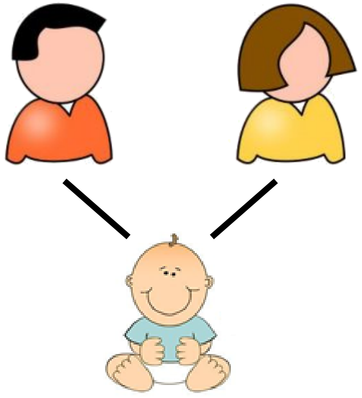
General techniques apply to many different scenarios for diagnosing Mendelian diseases



Identify causal gene for a rare disease
given a small patient cohort



Identify patients with the same
rare functional mutation at two different hospitals



Identify rare functional variants
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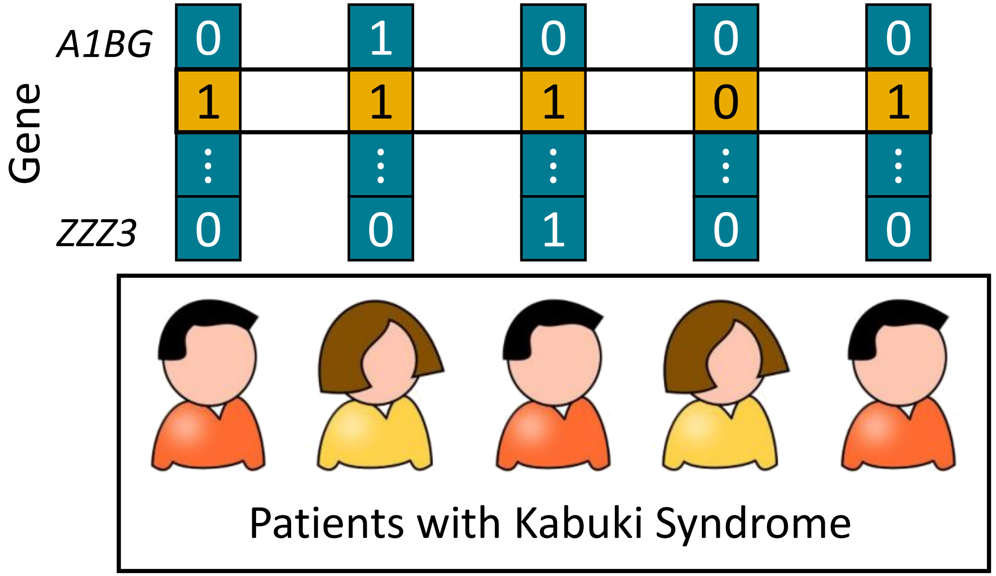

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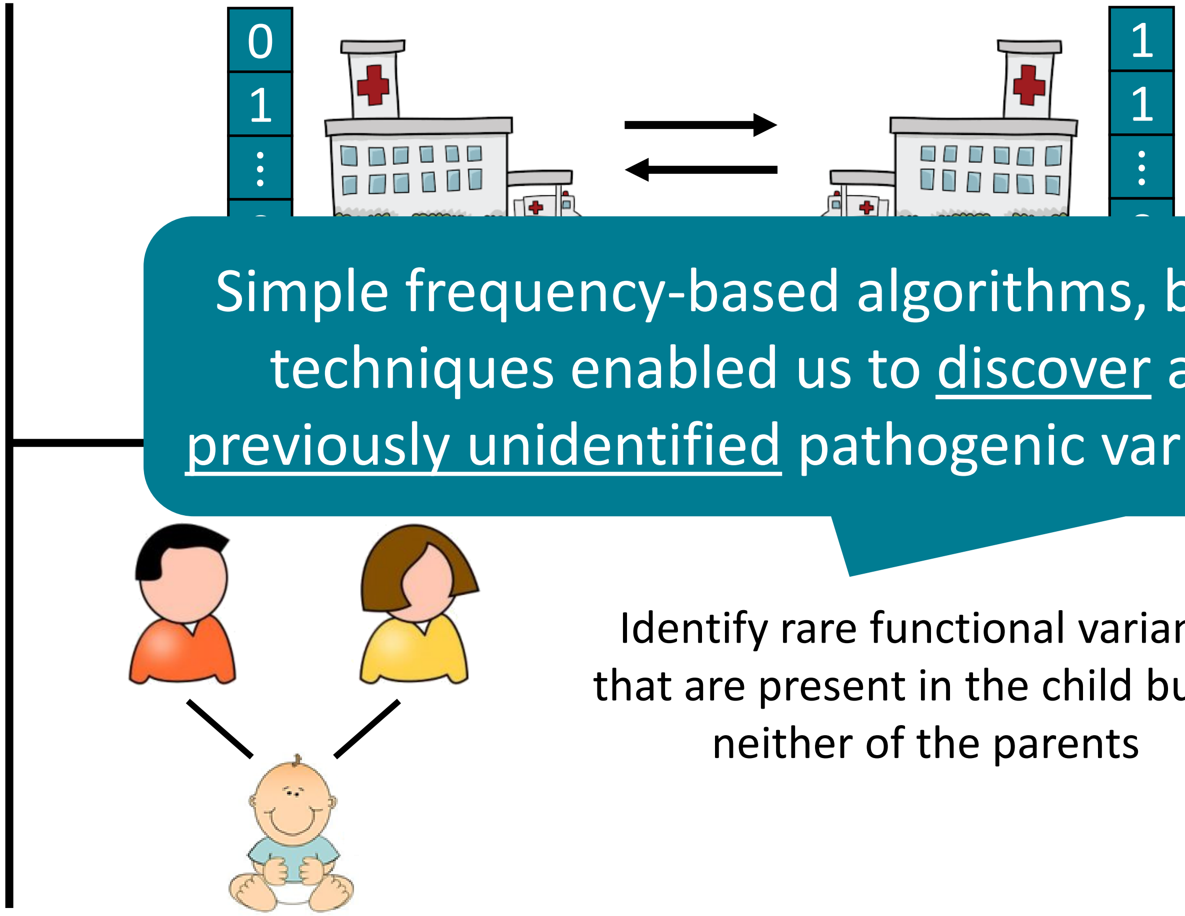


Simple frequency-based algorithms, but techniques enabled us to <u>discover</u> a <u>previously unidentified</u> pathogenic variant

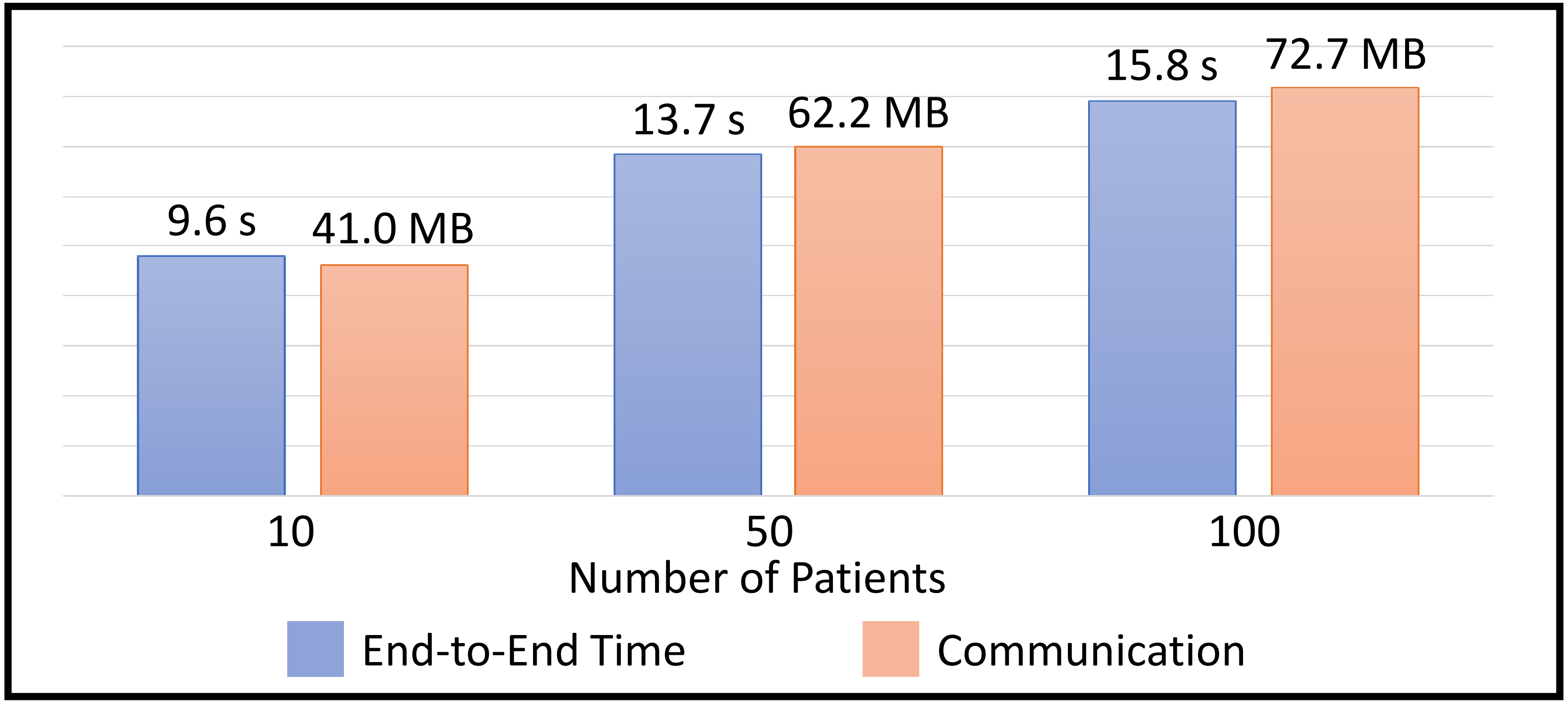
Identify rare functional variants that are present in the child but in neither of the parents

Rare Disease Diagnosis

Jagadeesh-W-Birgmeier-Boneh-Bejerano [Science 2017]

Experimental benchmarks for identifying causal gene in small disease cohort

- Simulated two non-colluding entities with 1 server on East Coast and 1 on West Coast



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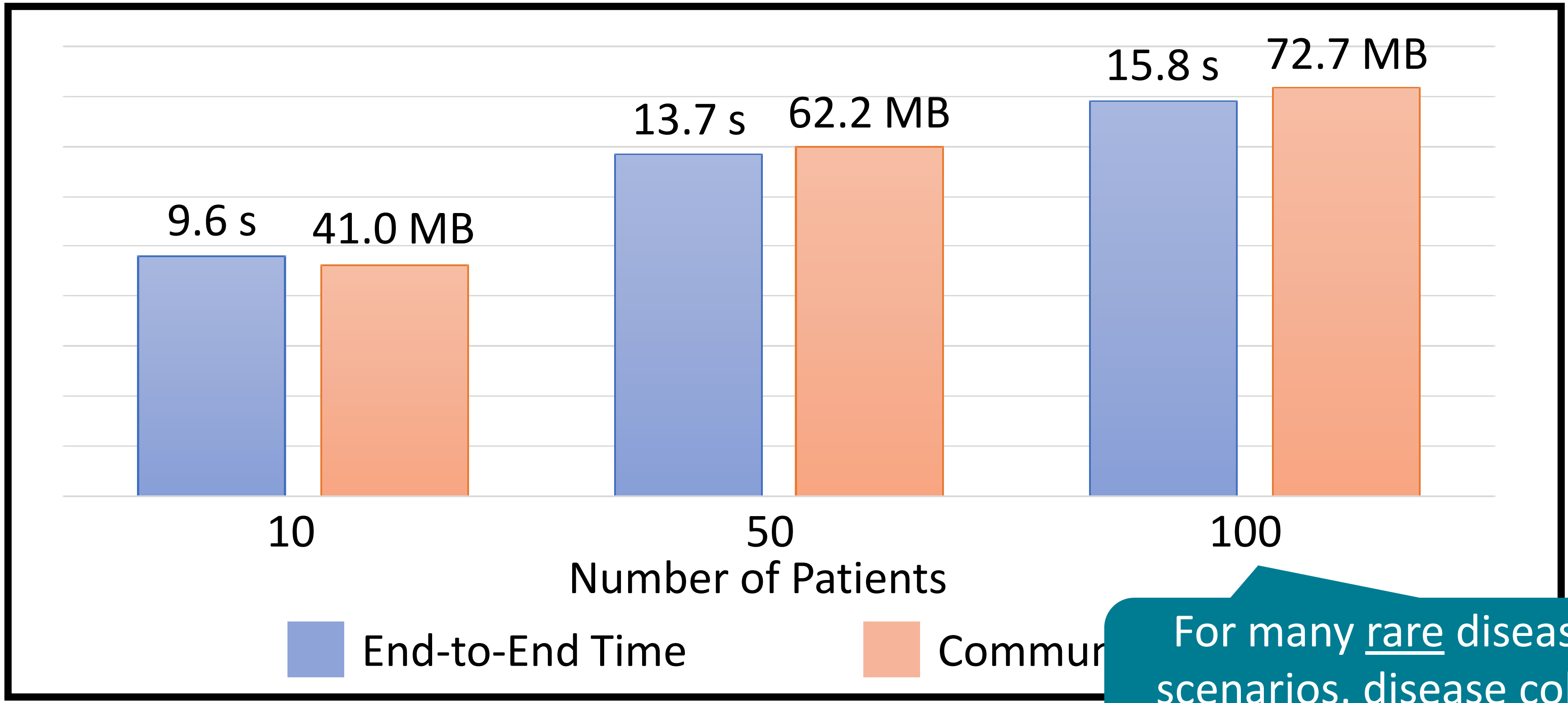
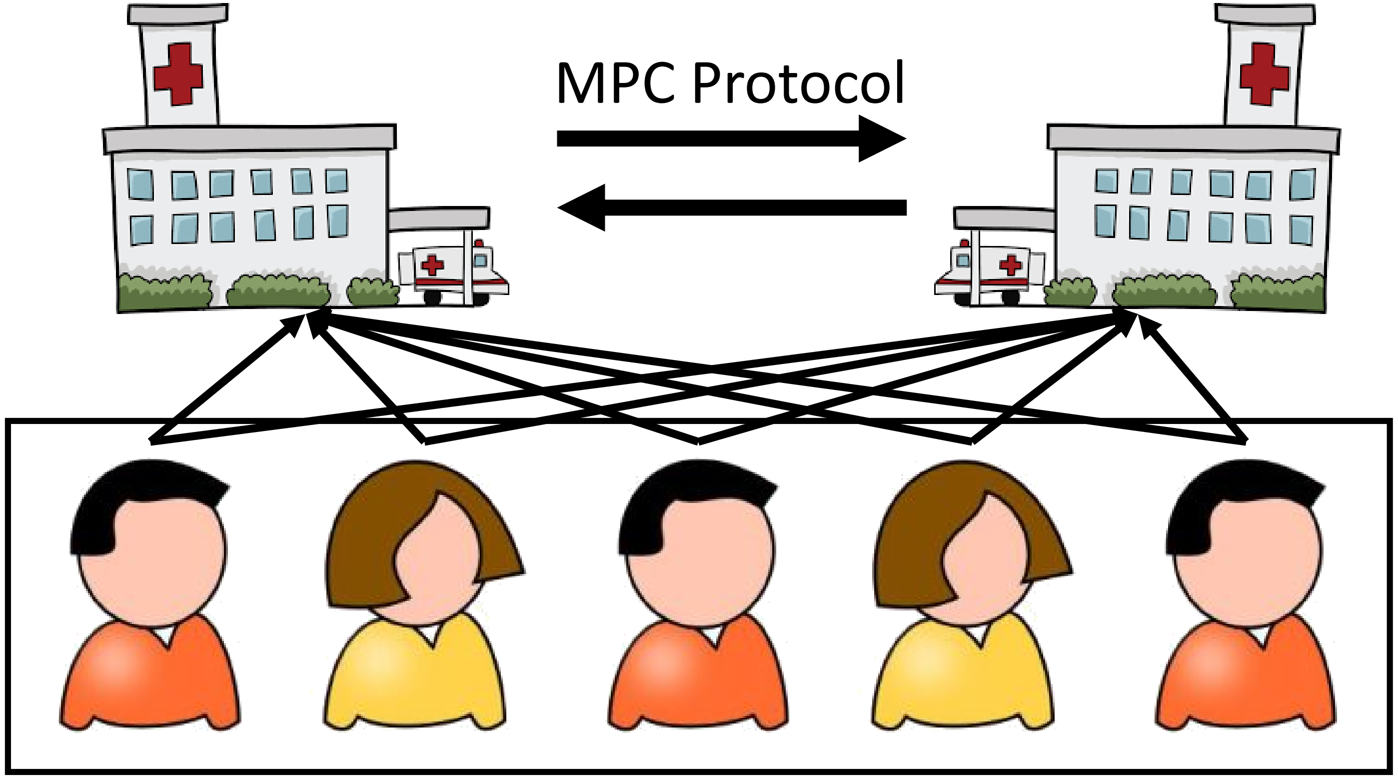


For many rare disease diagnosis scenarios, disease cohort size can be very small (e.g., 5-10 patients)

Secure Genome Computation



Modern cryptographic tools enable useful computations while protecting the privacy of individual genomes

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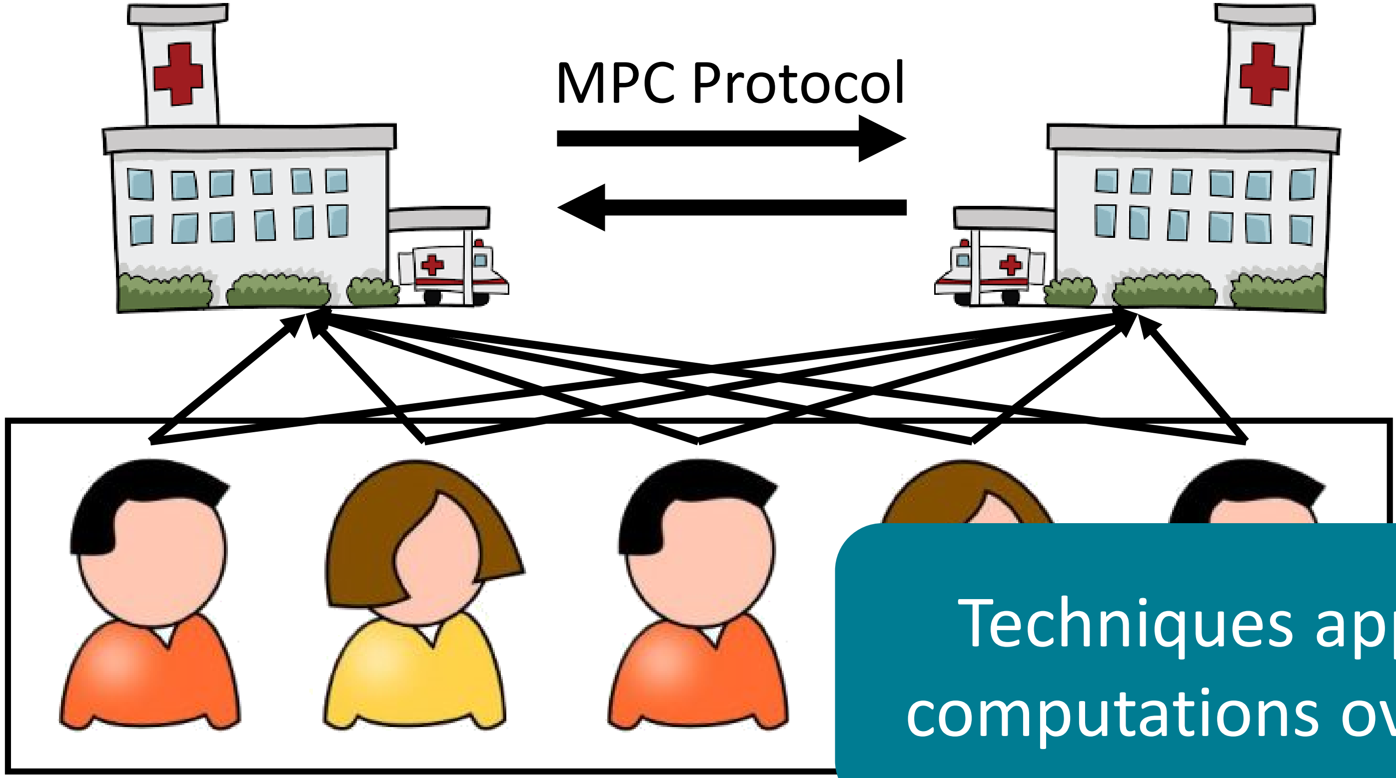
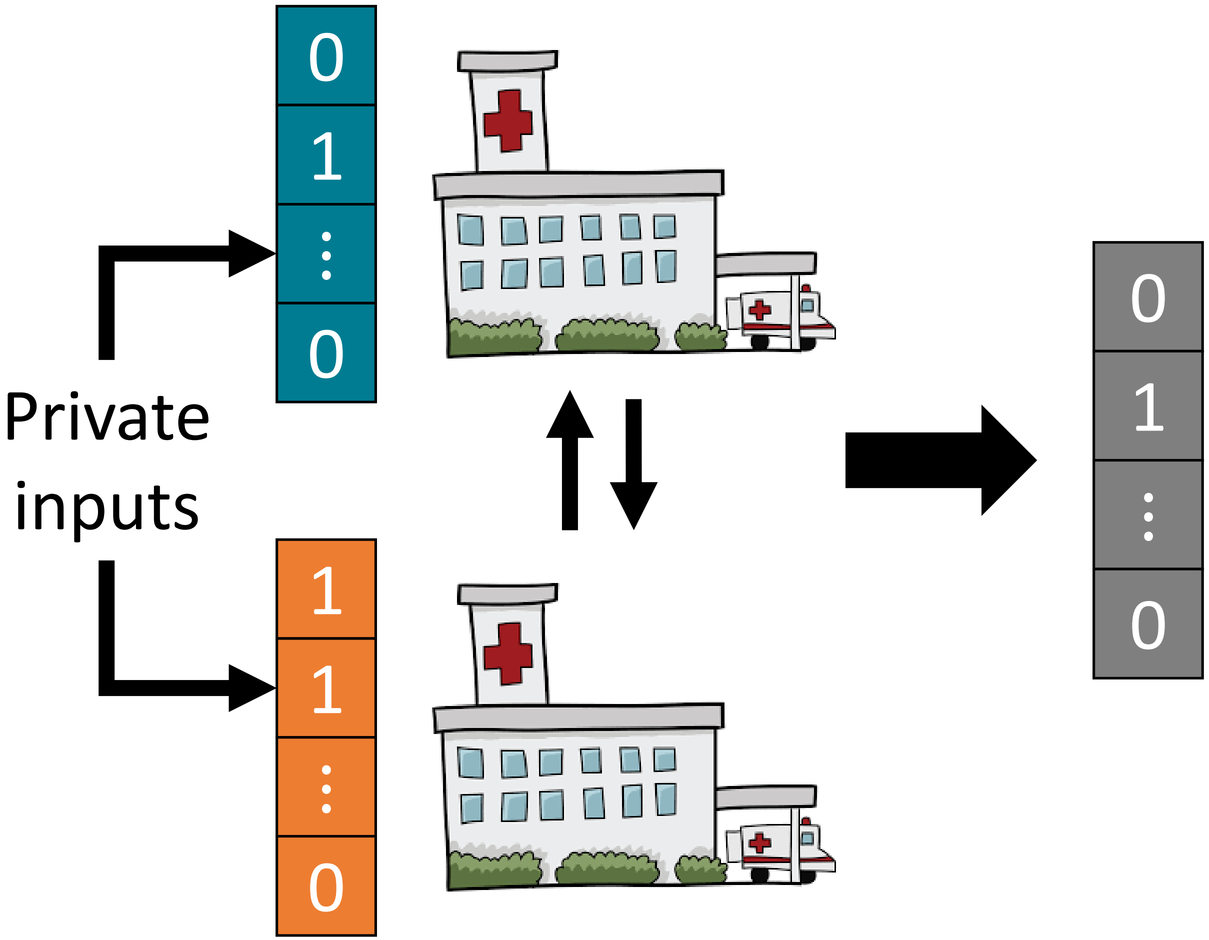


Techniques apply to general computations over private data

Modern cryptographic tools enable useful computations while protecting the privacy of individual genomes

Yao’s Protocol for Two-Party Computation

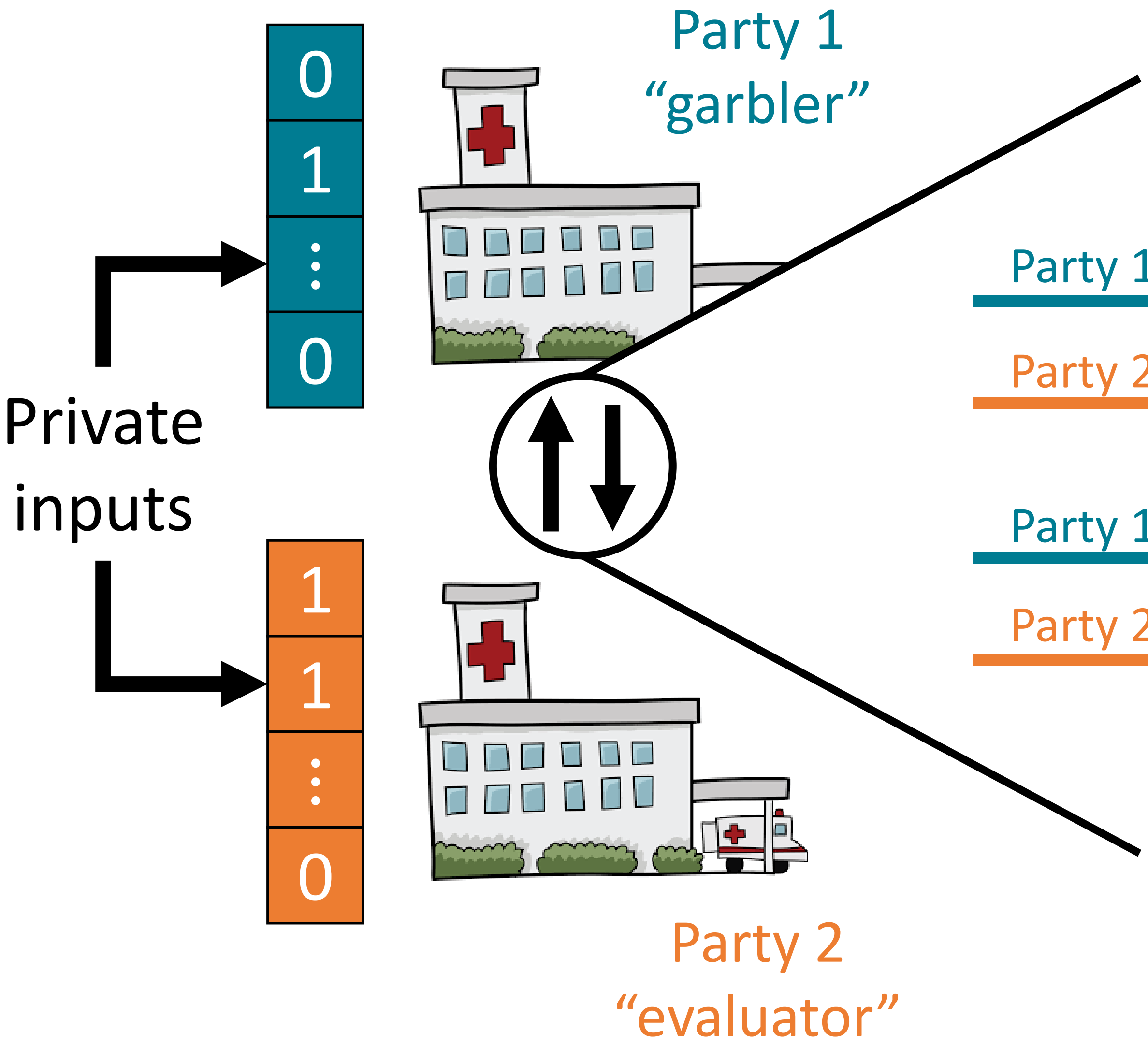
Yao's Protocol for Two-Party Computation [Yao82]



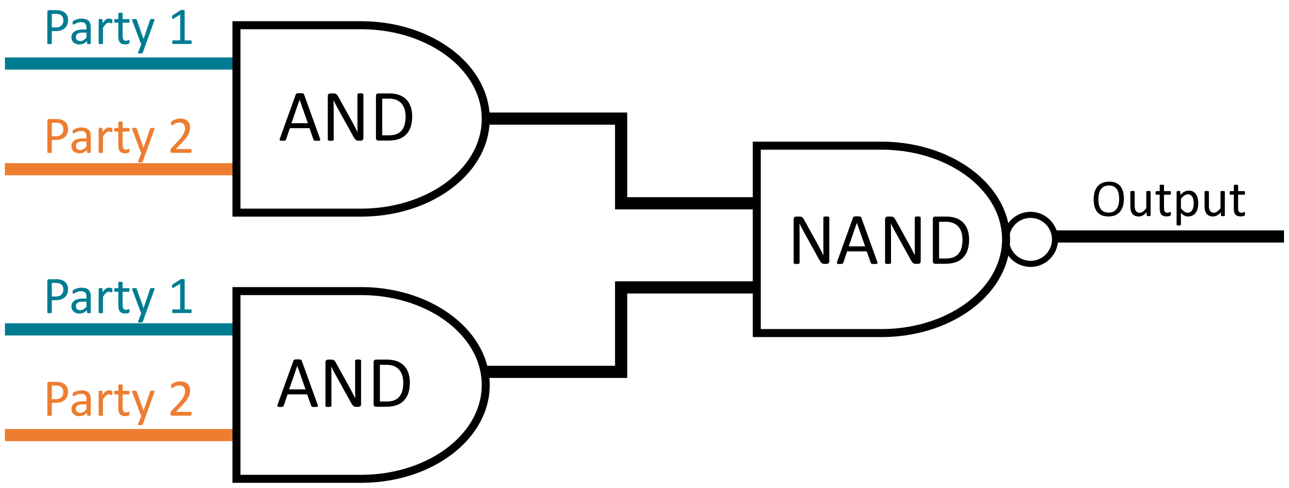
Security guarantee: everything the parties learn can be inferred from the output and their individual inputs

Classic protocol for two-party computation

Yao's Protocol for Two-Party Computation [Yao82]

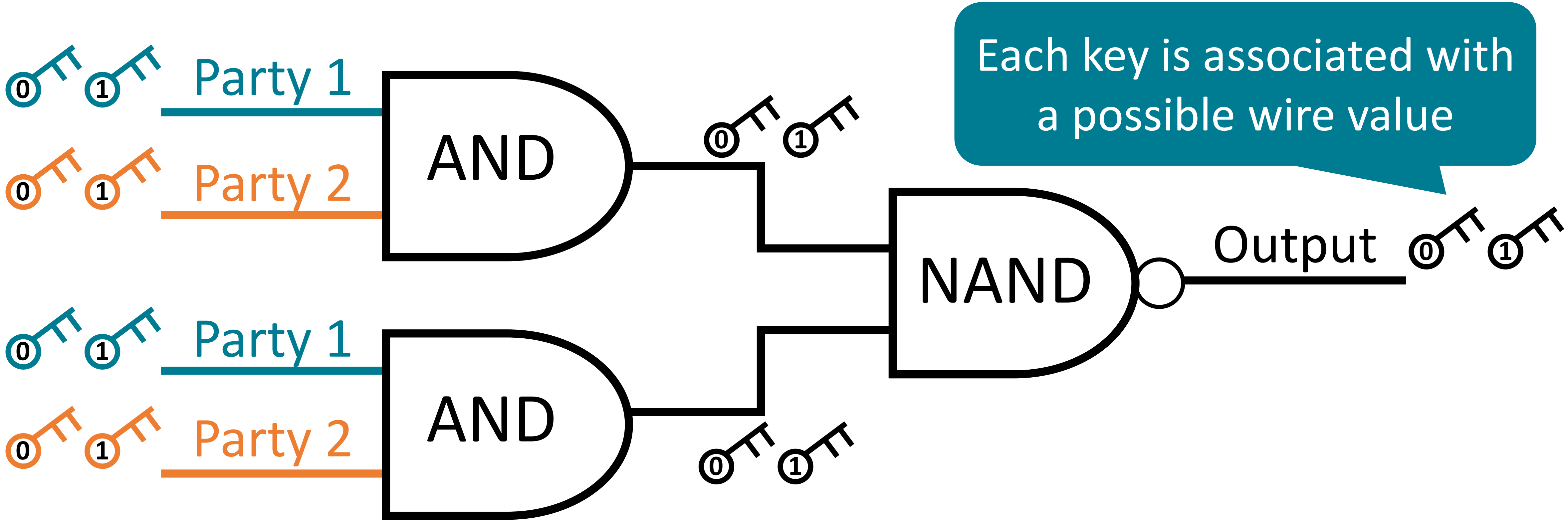


Step 1: Model computation as a Boolean circuit



Yao's Protocol for Two-Party Computation [Yao82]

Step 2: Garbler "encrypts" the circuit (i.e., "garbles" the circuit)



Garbler chooses two different encryption keys for every wire in the circuit

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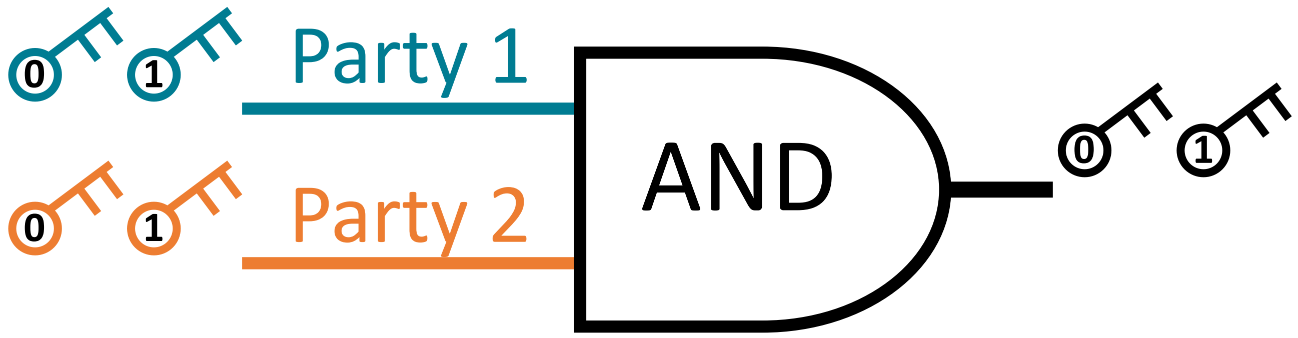

Inputs: Party 1	Inputs: Party 2	Output
0	0	0
0	1	0
1	0	0
1	1	1

Idea: Encrypt the output key (for the output wire) with the two input keys (for the input wires)

Garbler constructs a garbled truth table for each gate in the circuit

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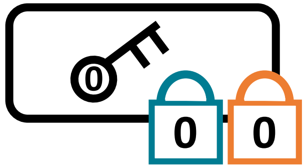

$$\mathrm{Enc}\left(k_0^{(1)}, \mathrm{Enc}\left(k_0^{(2)}, k_0^{(\mathrm{out})}\right)\right)$$

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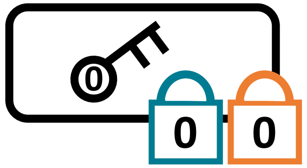

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Key for party 1's input

Key for party 2's input

Key for output wire

Inputs		Output
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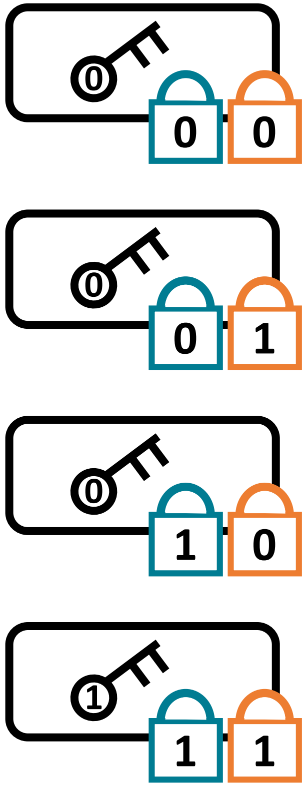

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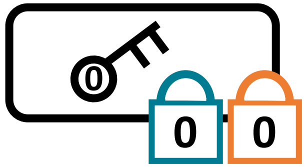

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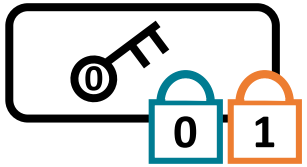

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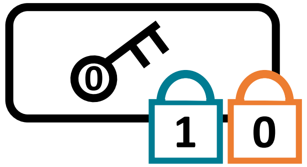

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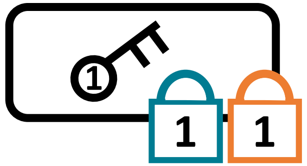

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Garbled truth table randomly permuted

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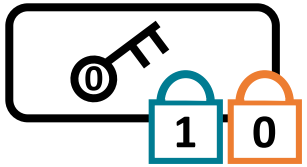

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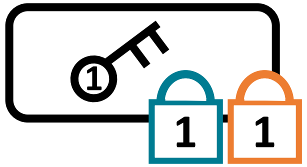

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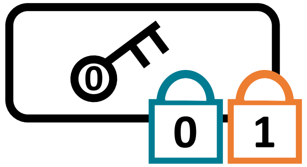

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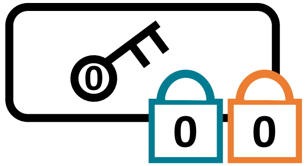

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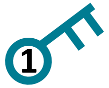
Garbled truth table randomly permuted

Invariant: Given just a single key for each input wire, evaluator can learn a single key for the output wire



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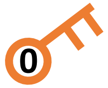

$k_0^{(2)}$

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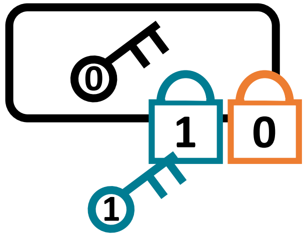

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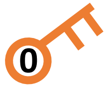
$k_1^{(1)}$ 

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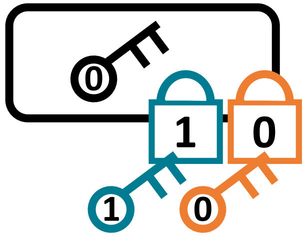

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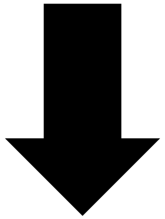

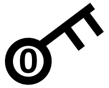

$k_0^{(\mathrm{out})}$

$k_0^{(\mathrm{out})}$ is just a symmetric key – does not reveal what the output bit is

Garbled truth table randomly permuted

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$k_1^{(1)}$ $k_0^{(2)}$

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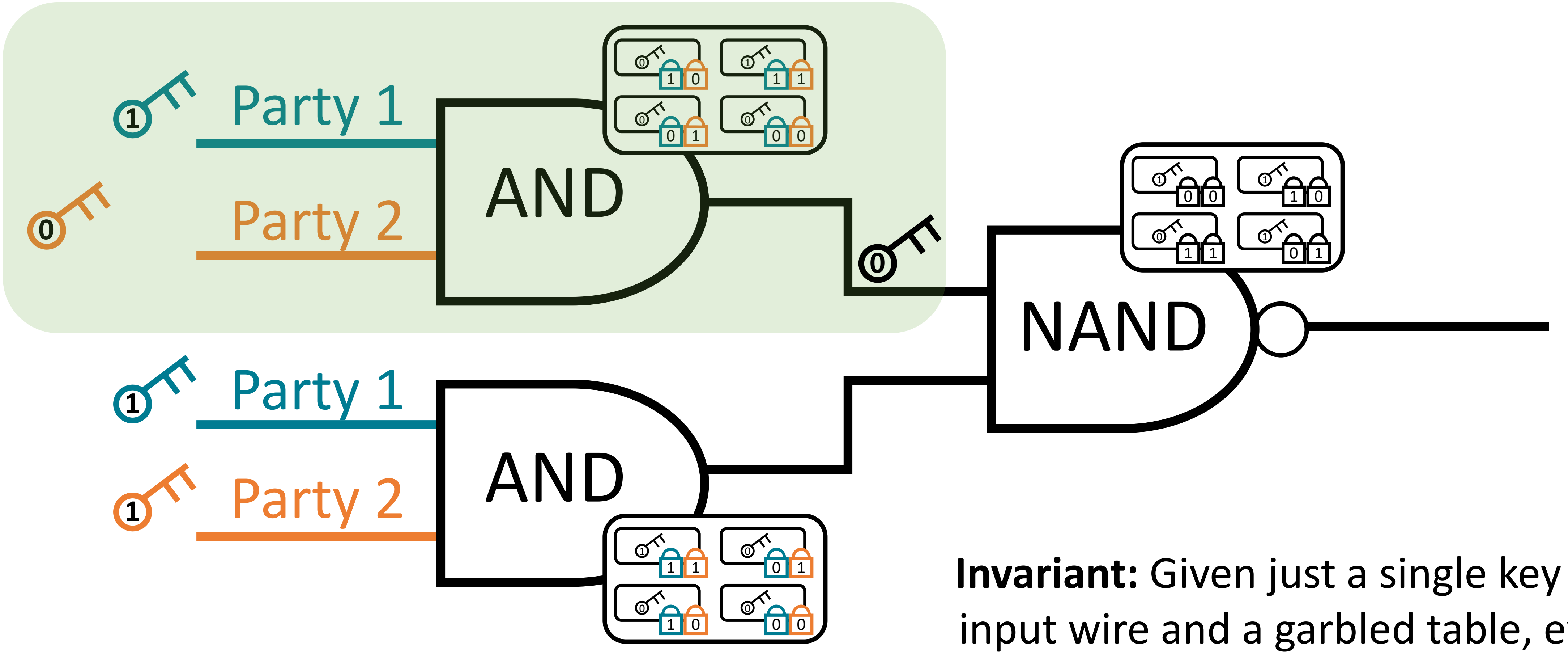

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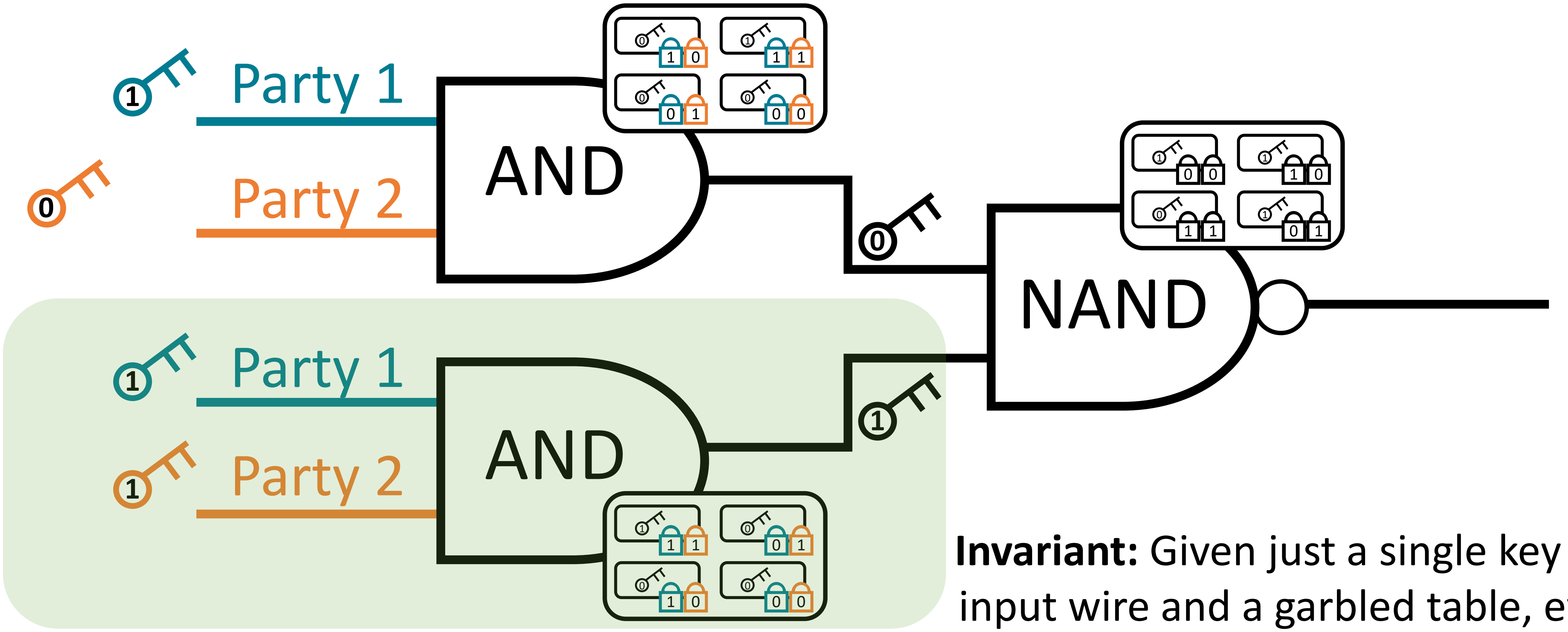

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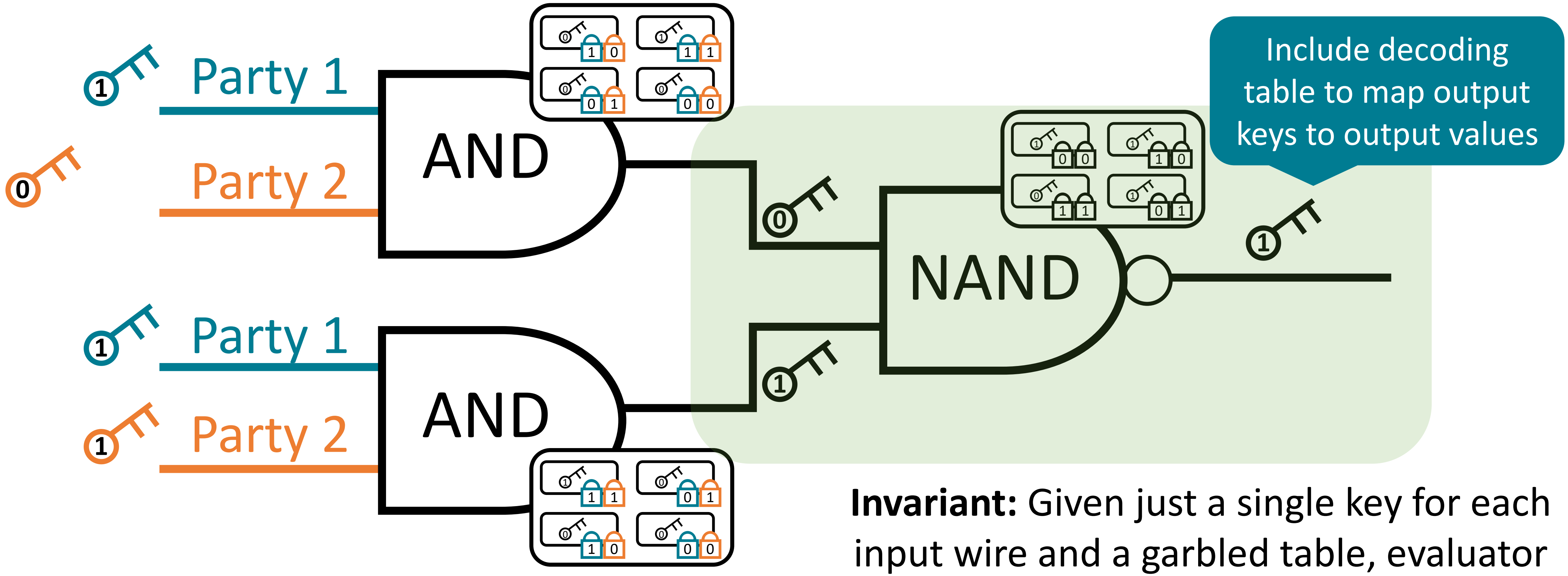

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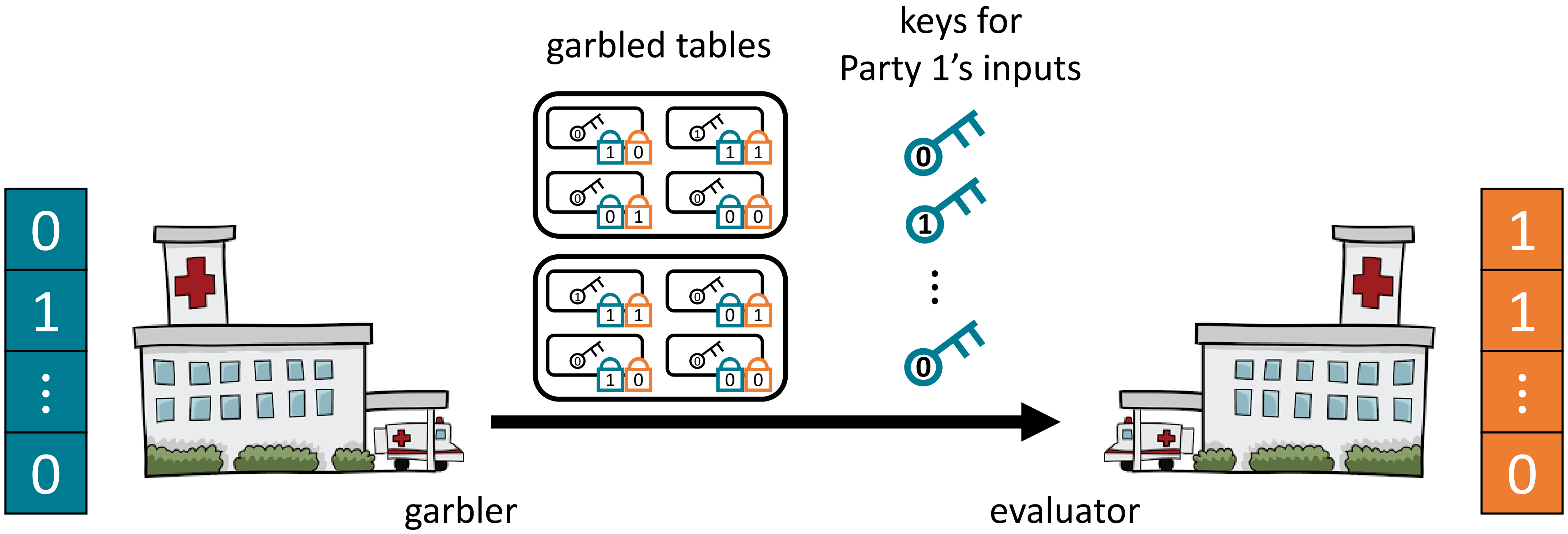
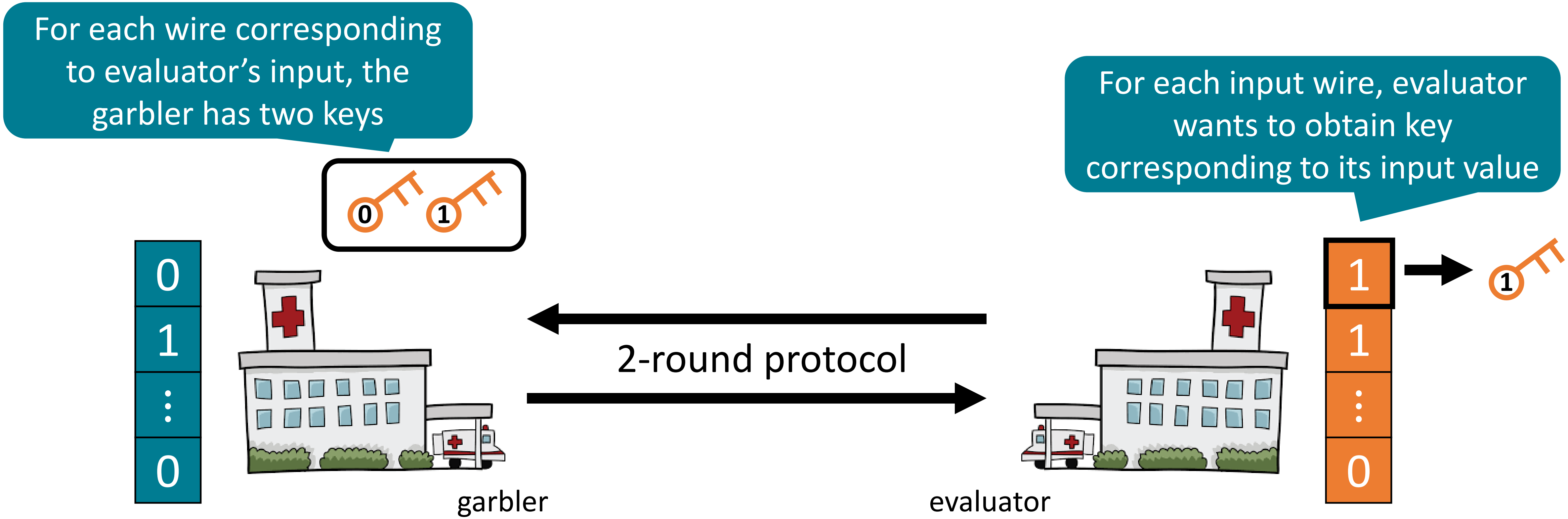


Question: how does evaluator obtain keys for its input?

Garbler can send garbled truth tables and keys for its inputs

Yao's Protocol for Two-Party Computation [Yao82]

Step 3: Evaluator uses "oblivious transfer" to obtain keys for its input

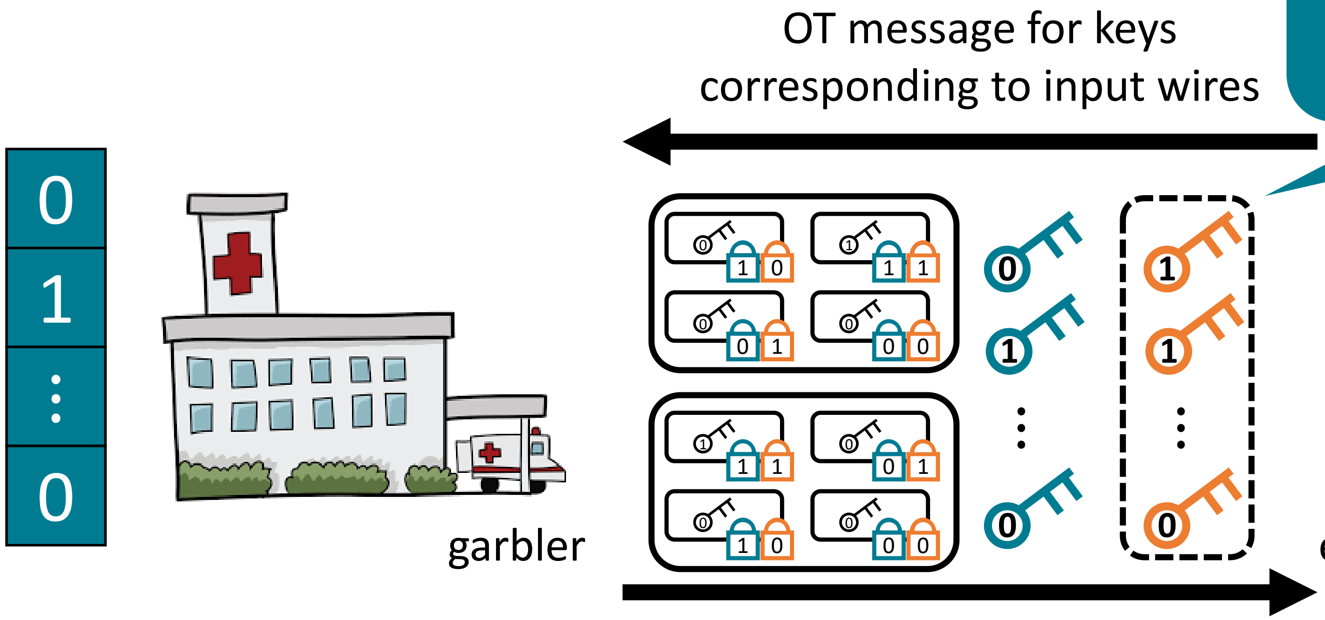


At the end of the oblivious transfer protocol, garbler learns nothing about which key evaluator obtains, and evaluator learns exactly one of the two keys

Yao's Protocol for Two-Party Computation [Yao82]

Two-round protocol for secure two-party communication

Keys communicated using OT (garbler does not know which keys are transmitted)

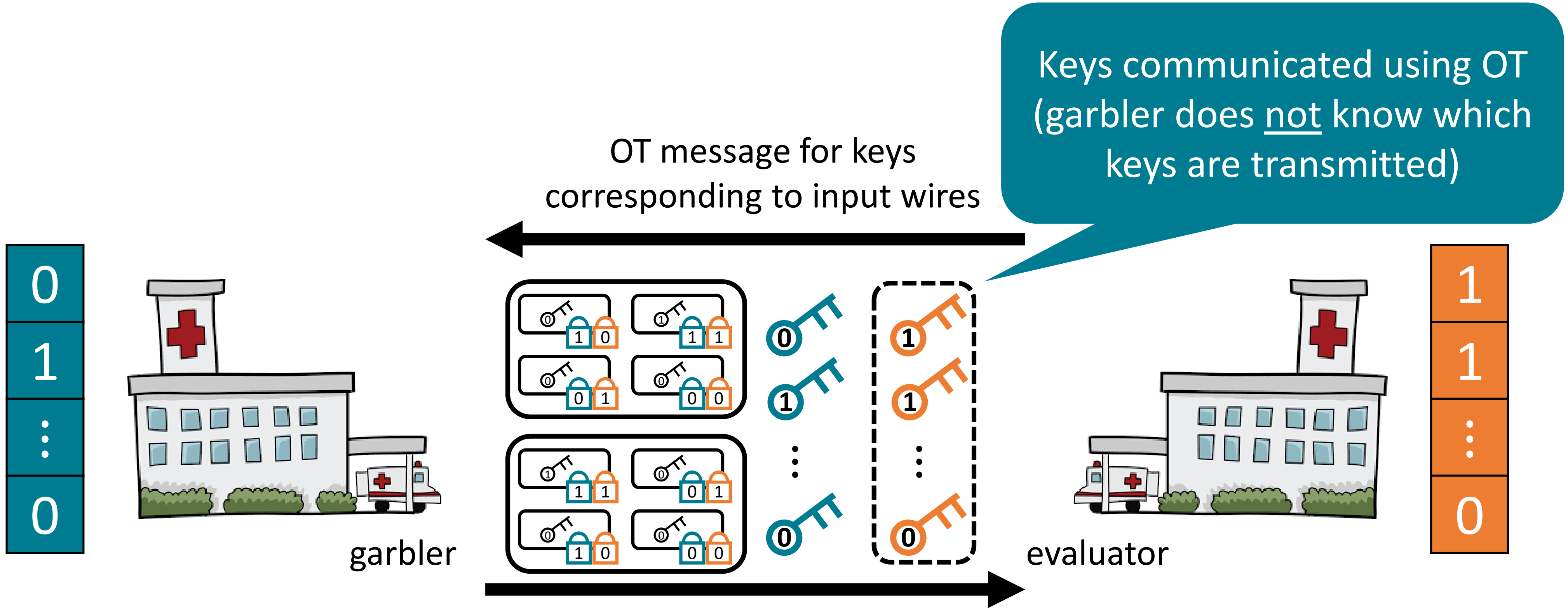


Many improvements are possible to achieve better performance

Evaluator uses keys to evaluate circuit gate-by-gate

Yao's Protocol for Two-Party Computation [Yao82]

Two-round protocol for secure two-party communication



Many improvements are possible to achieve better performance

Protocol is very efficient; communication is the bottleneck

The Story So Far…

Jagadeesh-W-Birgmeier-Boneh-Bejerano [Science 2017]

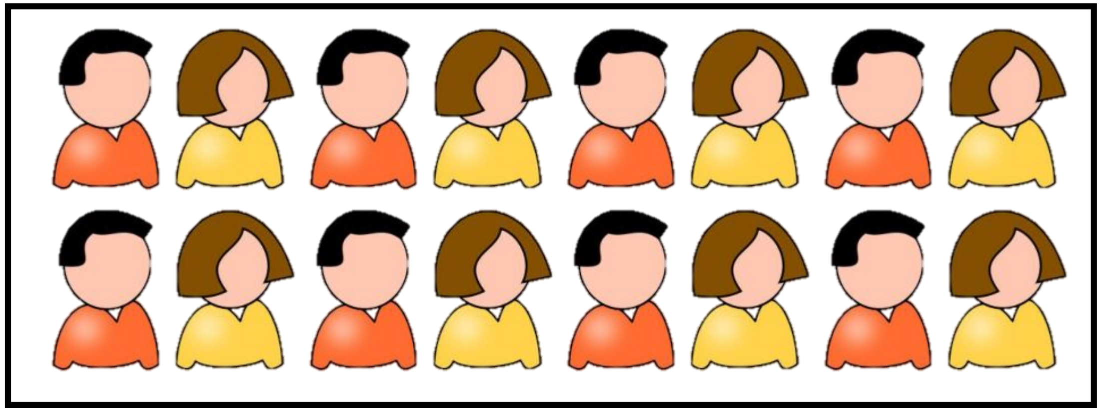
General techniques apply to many different scenarios for diagnosing Mendelian diseases

Simple frequency-based filters are useful for rare disease diagnosis and can be efficiently evaluated in a privacy-preserving manner

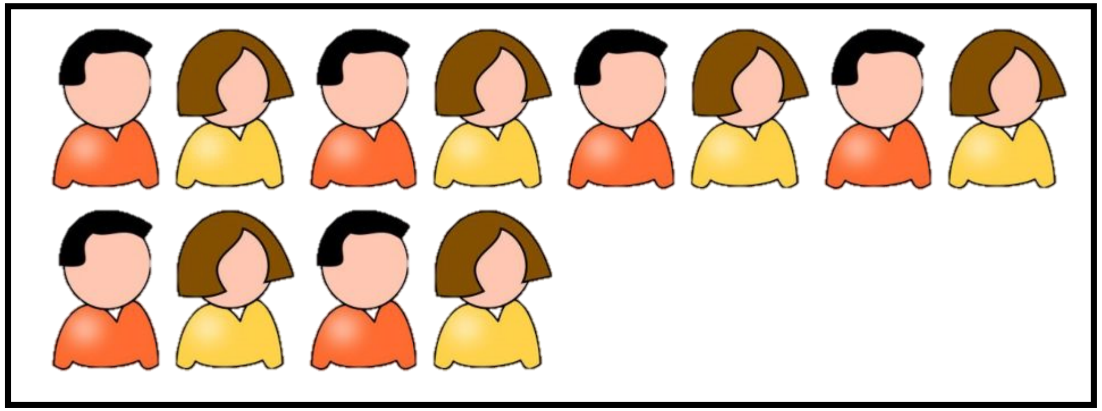
given a small patient cohort

But What About More Complex Diseases?

Cho-W-Berger [Nature Biotechnology 2018]



Control group (healthy)



Case group (affected)

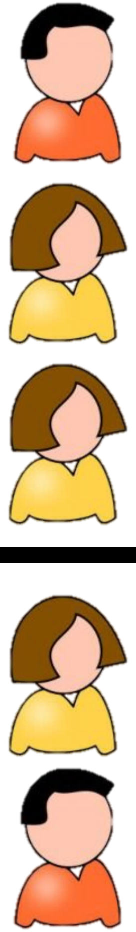
Genome-wide association studies (GWAS):

- Identify genetic variants most correlated with a particular disease (or particular phenotype)
- Oftentimes, focused on identifying complex interactions between many variants

But What About More Complex Diseases?

Cho-W-Berger [Nature Biotechnology 2018]

Each patient has a vector of <u>SNPs</u> (variations in specific locations in genome – 3 types)



								Disease status
0	1	0	0	2	2	⋯	1	0
0	1	1	0	2	2	⋯	1	0
1	1	0	0	2	2	⋯	0	0
2	1	1	2	2	0	⋯	0	1
2	1	0	2	2	1	⋯	1	1

Goal: identify SNPs that are most correlated with disease status

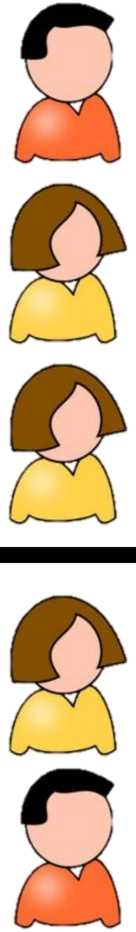
Healthy individuals

Patients with lung cancer

But What About More Complex Diseases?

Cho-W-Berger [Nature Biotechnology 2018]

Each patient has a vector of SNPs (variations in specific locations in genome – 3 types)



								Disease status
0	1	0	0	2	2	…	1	0
0	1	1	0	2	2	…	1	0
1	1	0	0	2	2	…	0	0

Goal: identify SNPs that are most correlated with disease status

Healthy individuals

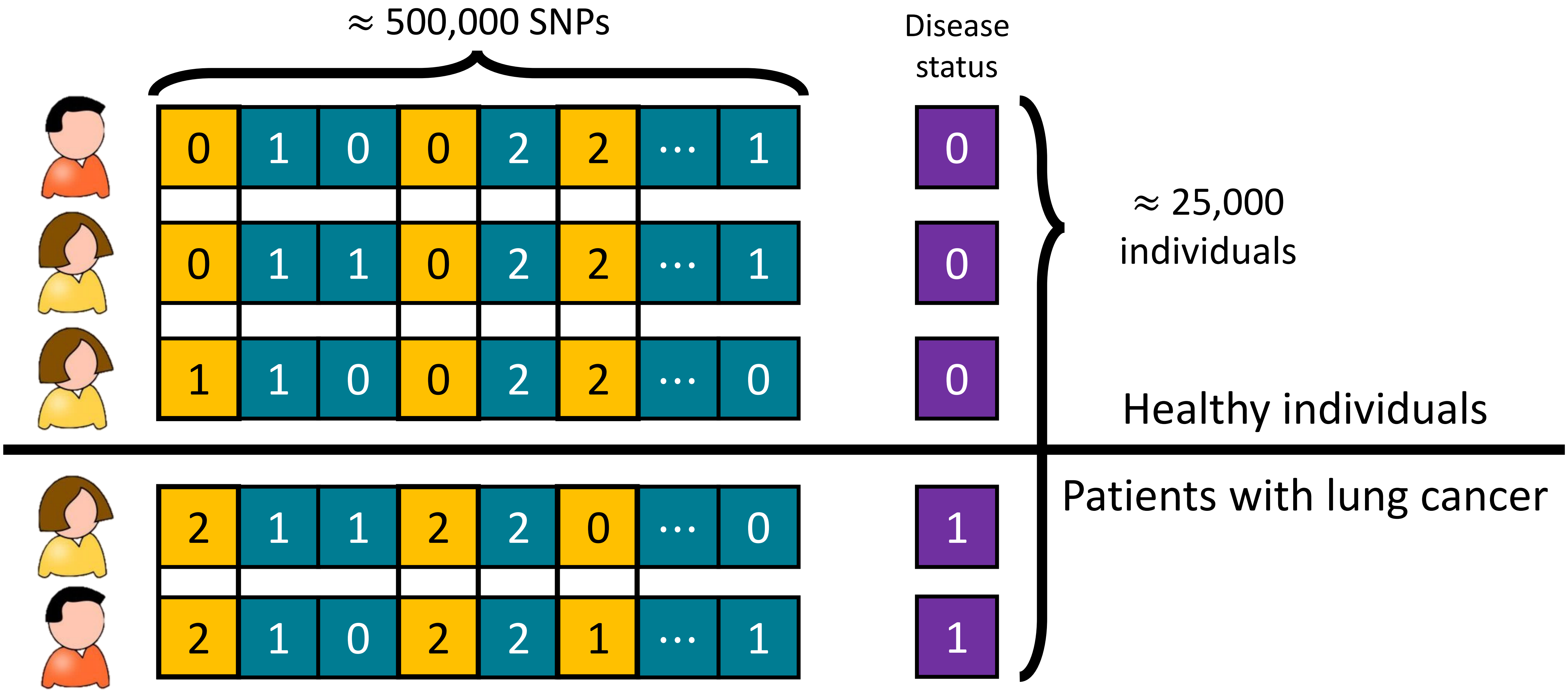
Patients with lung cancer

								Disease status
2	1	1	2	2	0	…	0	1
2	1	0	2	2	1	…	1	1

Unlike Mendelian diseases, we are looking for *many* associations (e.g., several hundred)

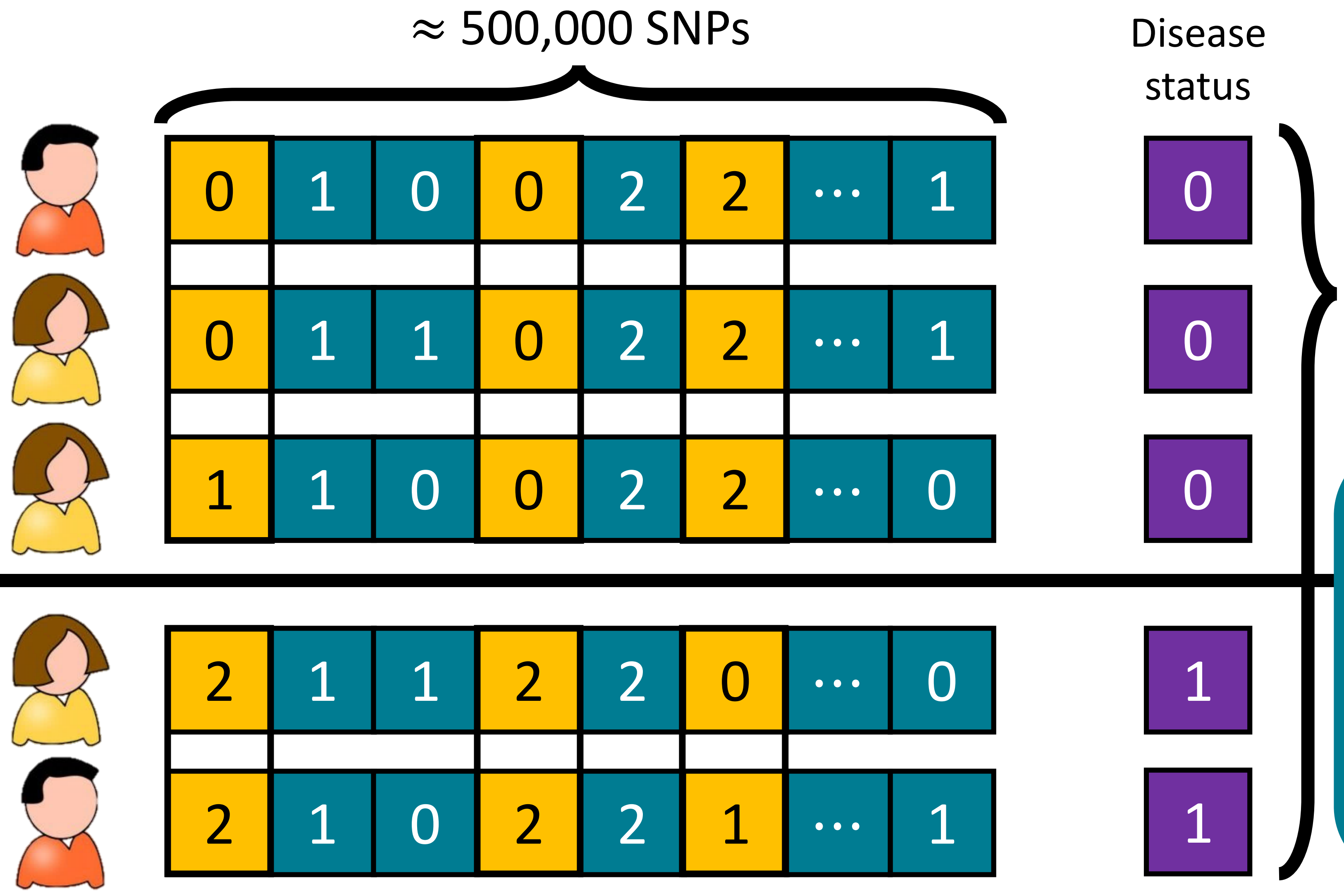
But What About More Complex Diseases?

Cho-W-Berger [Nature Biotechnology 2018]



But What About More Complex Diseases?

Cho-W-Berger [Nature Biotechnology 2018]

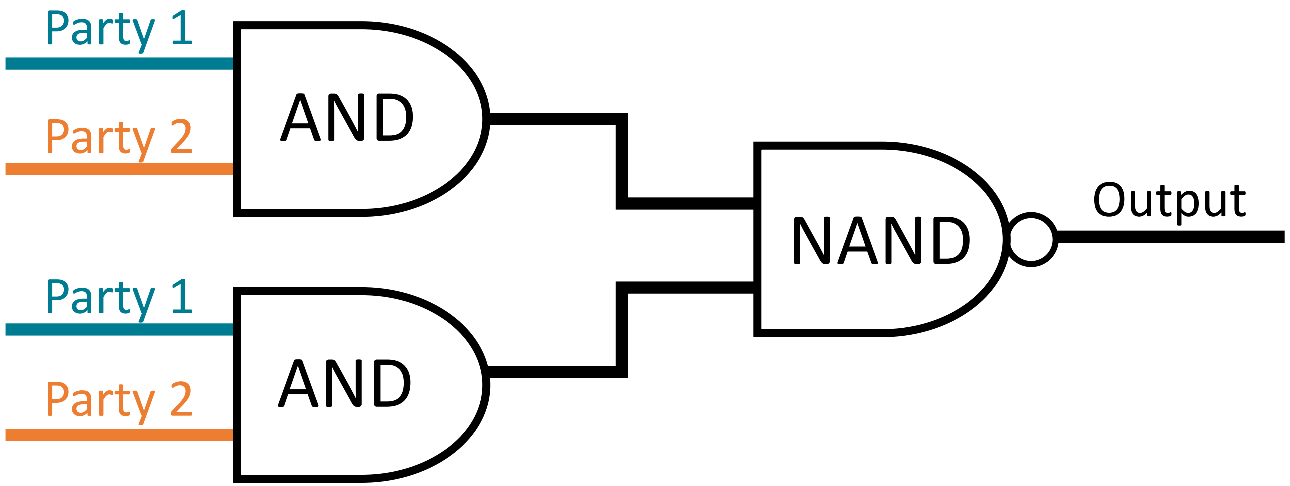


≈ 25,000 individuals

Challenge: in real GWAS studies, we need to correct for *population-level* differences between groups

Arithmetic Computations on Shared Data

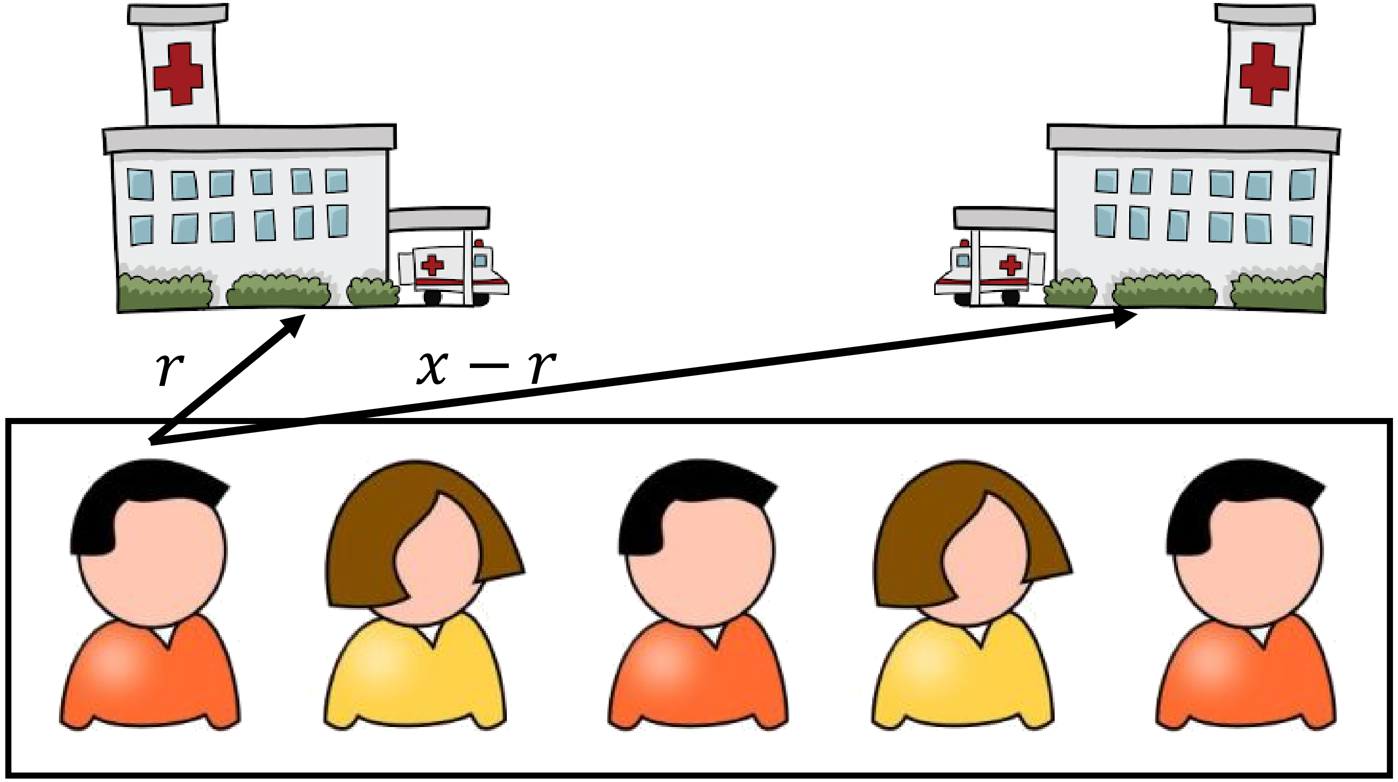
GWAS computations most naturally expressed as *arithmetic* computations (e.g., matrix operations)



Recall: to apply Yao's protocol, must first represent computation as a Boolean circuit

Can introduce significant overhead for arithmetic computations!

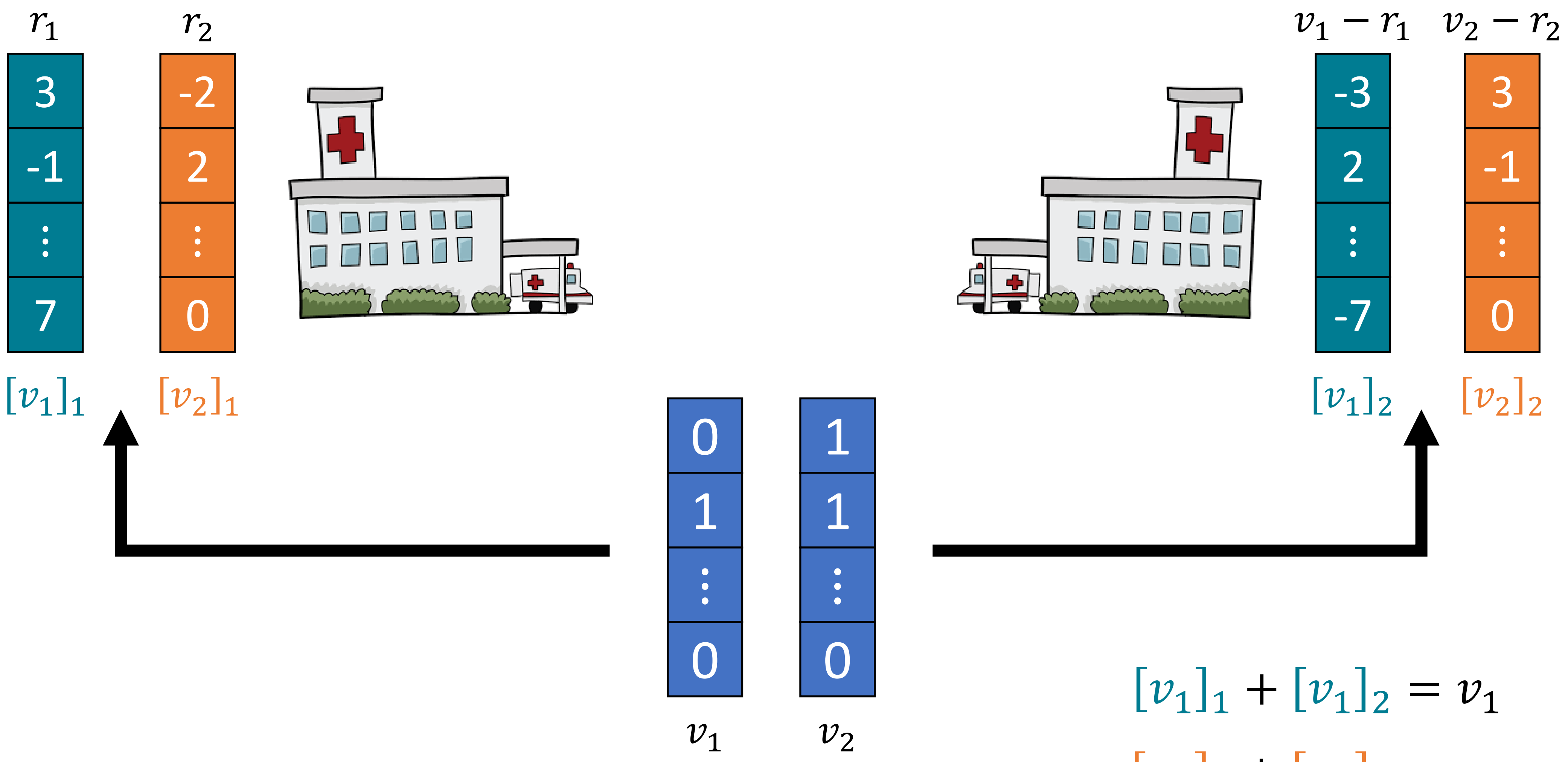
Arithmetic Computations on Shared Data



Patients "secret share" their data with two non-colluding hospitals

Approach: directly compute on secret-shared data

Arithmetic Computations on Shared Data



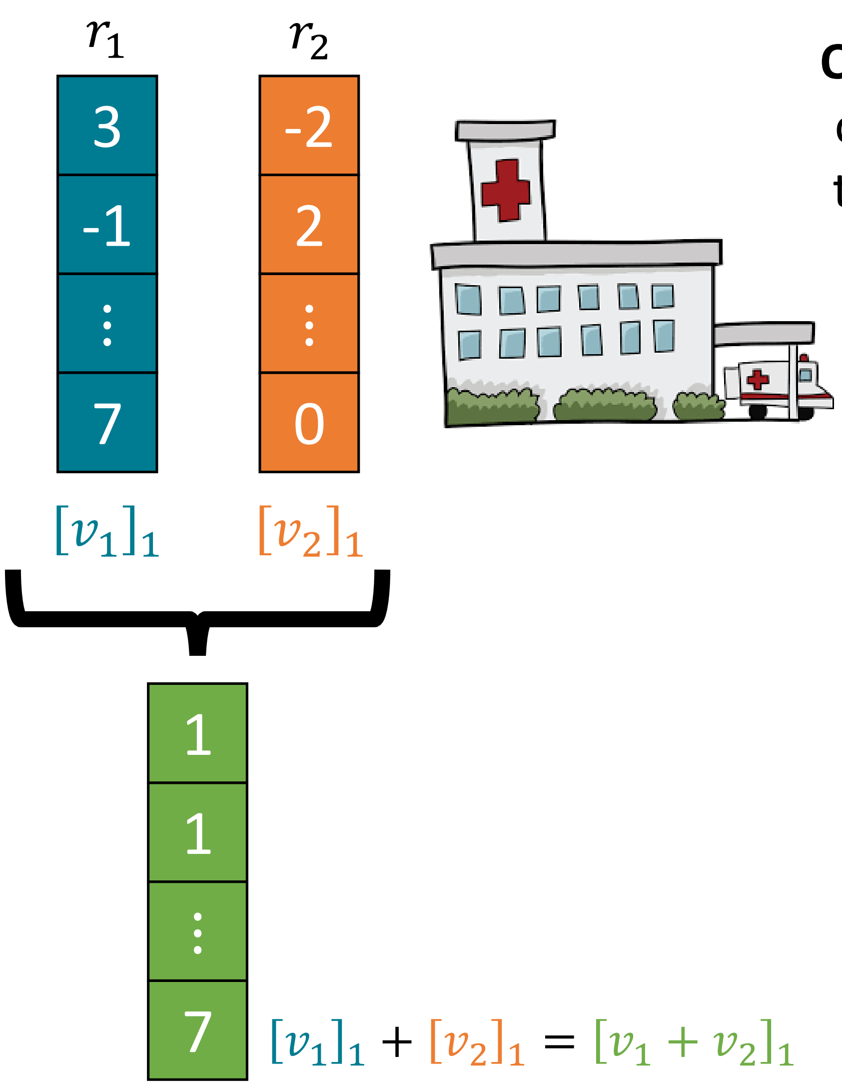
$$[v_1]_1 + [v_1]_2 = v_1$$

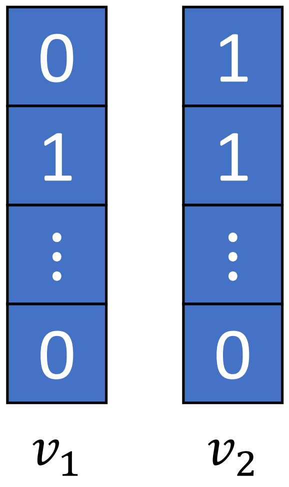
$$[v_2]_1 + [v_2]_2 = v_2$$

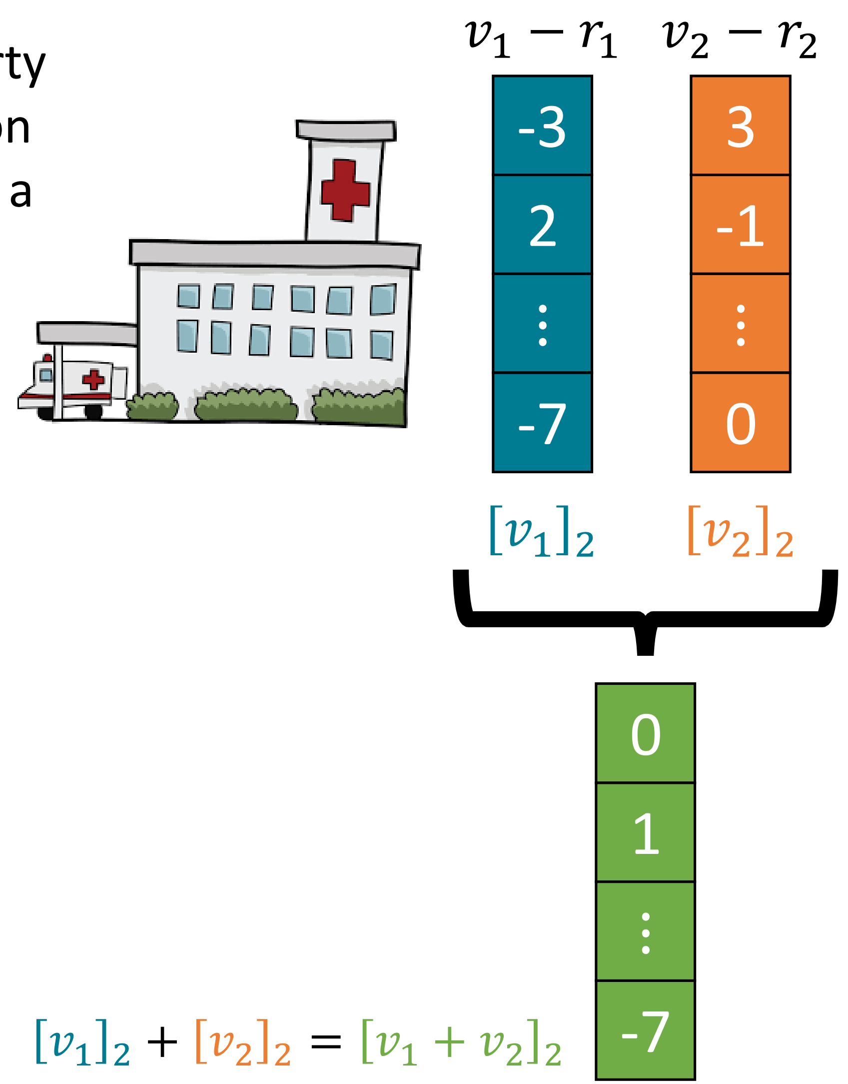
All operations done over a ring ($\mathbb{Z}_p$)

Arithmetic Computations on Shared Data

Observation: each party can locally compute on their shares to obtain a share of the sum



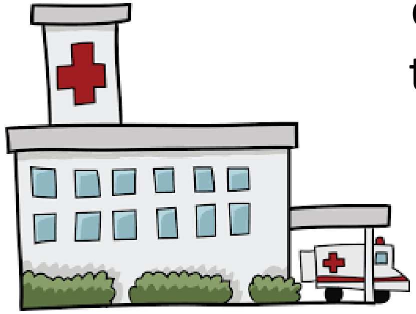




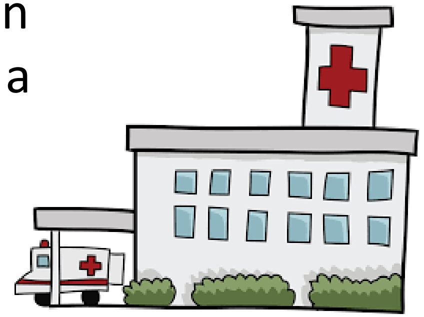
Arithmetic Computations on Shared Data

r_1: 3, -1, ⋮, 7 — $[v_1]_1$

r_2: -2, 2, ⋮, 0 — $[v_2]_1$



Observation: each party can locally compute on their shares to obtain a share of the sum



$v_1 - r_1$: -3, 2, ⋮, -7 — $[v_1]_2$

$v_2 - r_2$: 3, -1, ⋮, 0 — $[v_2]_2$

For computing products on shared values (e.g., matrix-vector products, inner products, etc.), we can use a single-round interactive protocol [Bea91]

1, 1, ⋮, 7

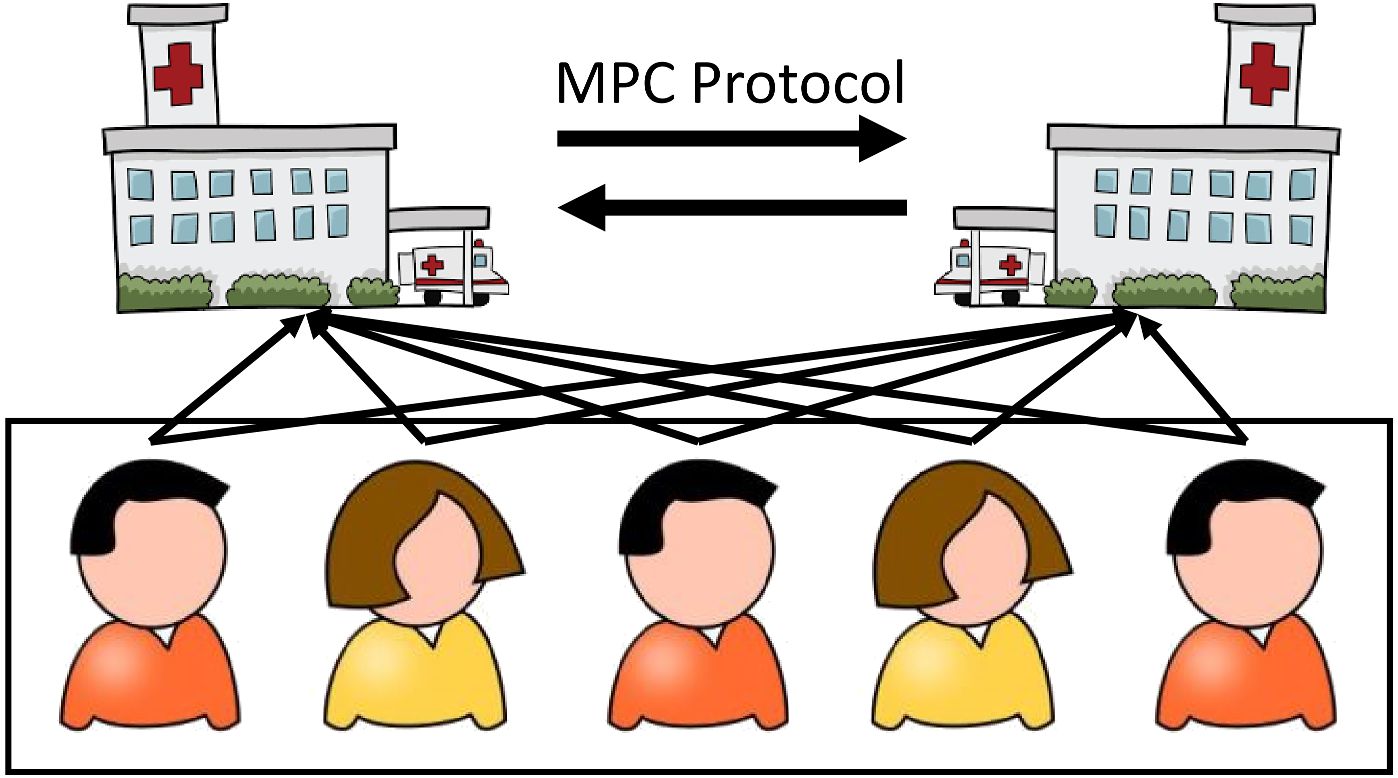
$[v_1]_1 + [v_2]_1 = [v_1 + v_2]_1$

$[v_1]_2 + [v_2]_2 = [v_1 + v_2]_2$

0, 1, ⋮, -7

What About More Complex Diseases?

Cho-W-Berger [Nature Biotechnology 2018]

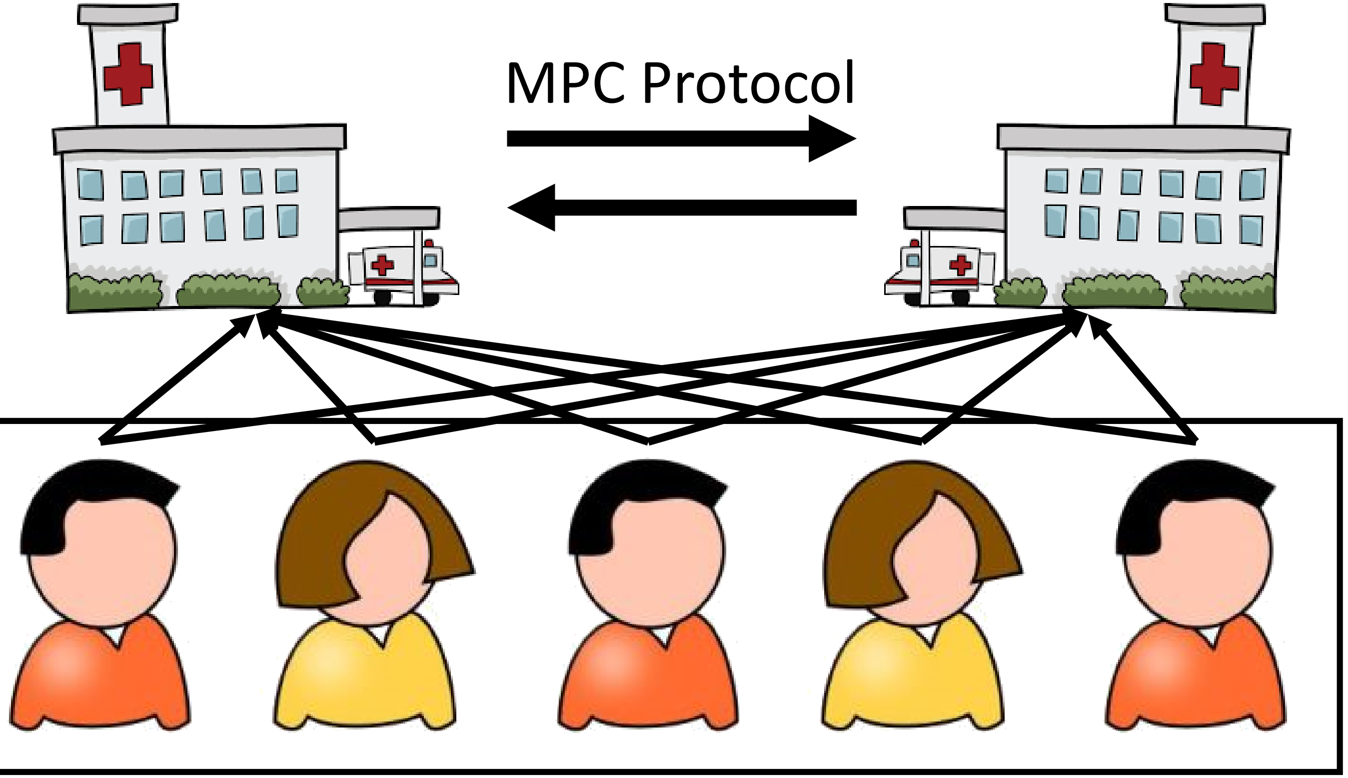


Approach: directly compute on secret-shared data

This work: first end-to-end GWAS protocol (with population correction)

- Based on computing on secret-shared inputs
- For 25K individuals, computation completes in about 3 days: feasible for performing large-scale scientific studies

Secure Genome Computation



Modern cryptographic tools enable useful computations while protecting the privacy of individual genomes

Secure Genome Computation

Many other techniques (with different tradeoffs):

- Homomorphic encryption (computing on encrypted data)
  [Zhang et al., 2015; Lauter et al., 2015, …]

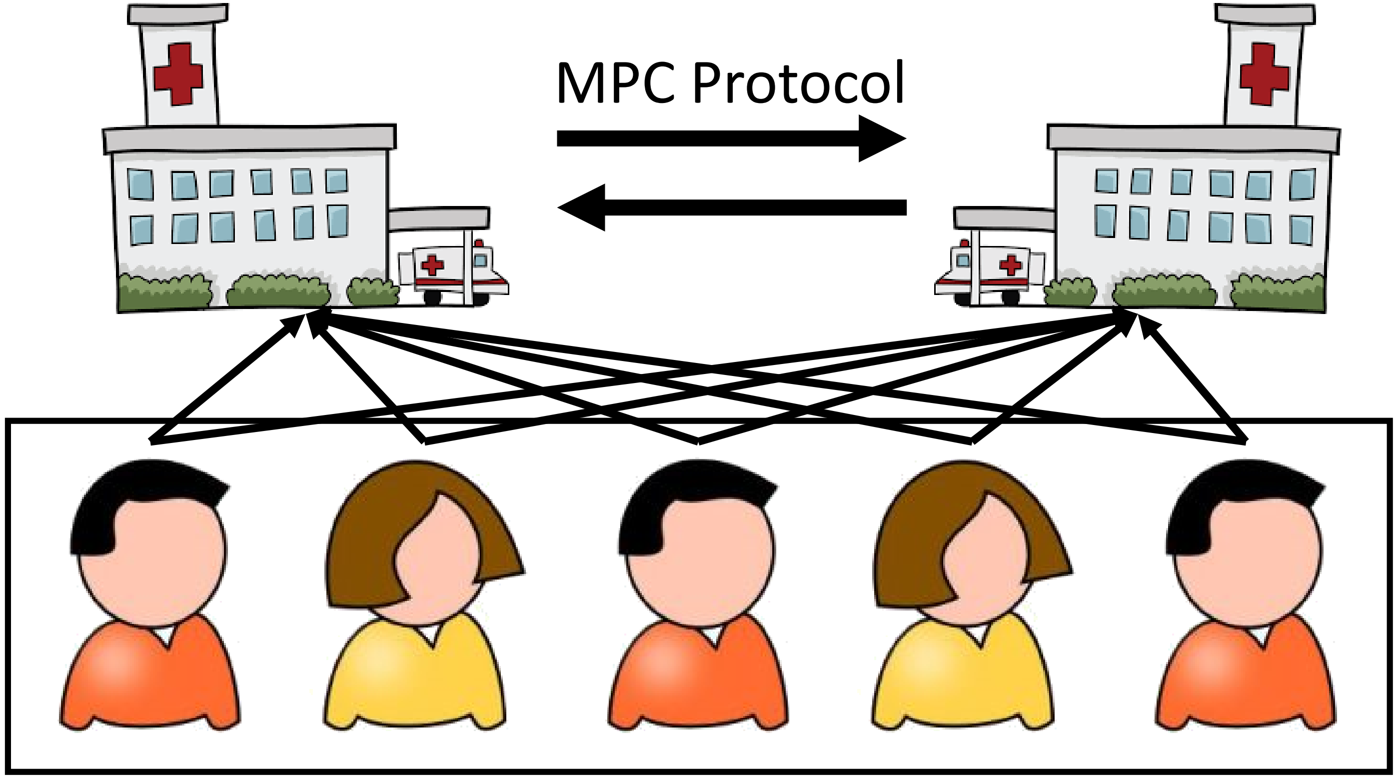
- Differential privacy (adding noise to protect privacy)
  [Simmons et al., 2016; Simmons-Berger, 2016, …]

- Intel SGX (leveraging secure hardware)
  [Chen et al., 2017; Wang et al., 2016; Chen et al., 2016, …]

[Not an exhaustive list!]

Modern cryptographic tools enable useful computations while protecting the privacy of individual genomes

Secure Genome Computation



Project Website:

https://crypto.stanford.edu/~dwu4/genomepriv-project.html

Thank you!