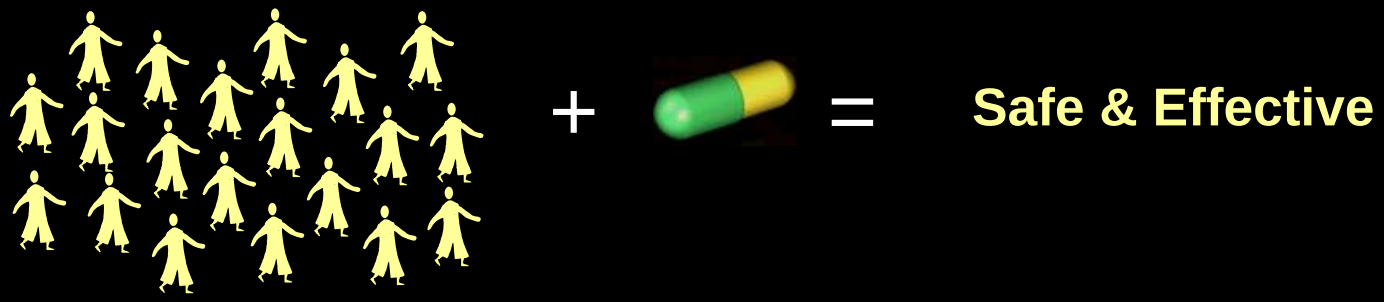
The Centre for Molecular Medicine and Therapeutics

Pharmacogenetics of Severe Adverse Drug Reaction

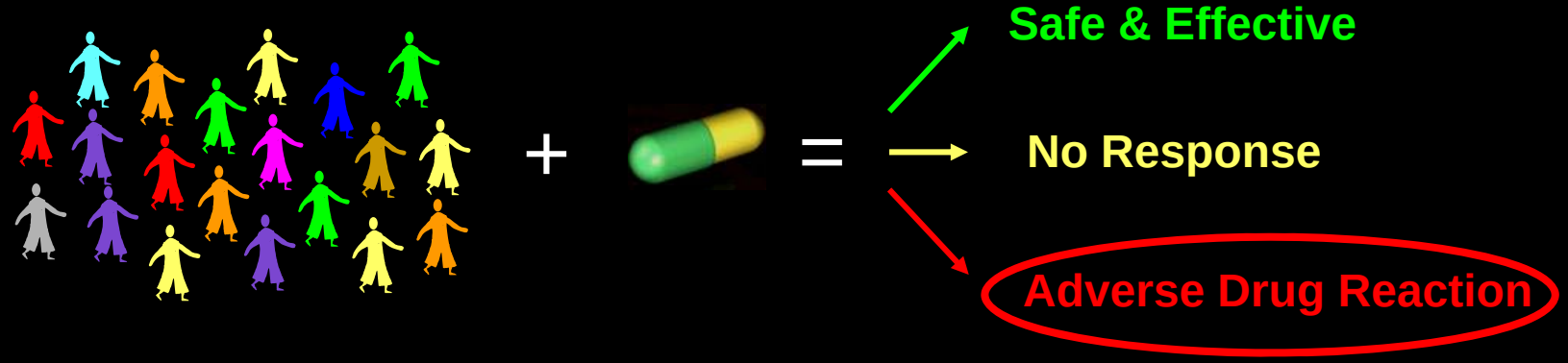
Colin Ross, PhD
Medical Genetics
CMMT, CFRI, UBC

Paradox of Modern Drug Development

1. Clinical trials provide evidence of efficacy and safety at <u>usual doses</u> in ***populations***



2. Physicians treat ***individual*** patients who can <u>vary widely</u> in their response to drug therapy



Adverse Drug Reactions

- 5th leading cause of death in the USA
  - Over 100,000 fatal ADRs in hospitalized patients each year
  - Over 2,000,000 serious ADRs in hospitalized patients (6.7%)/yr
- ADRs cause 7% of all hospital admissions (UK)
- ADR Health care costs: $78-177 billion annually (USA)
  - **Exceeds the annual cost of medications**
- ADRs cause an average 2 day increase in hospital stays
- **95%** of all ADRs are unreported

THE VANCOUVER SUN

BREAKING NEWS AT vancouversun.com

EDITION SERIOUSLY WESTCOAST SINCE 1912 TUESDAY, JUNE 3, 2008

ABBOTSFORD GANGSTERS FACE CHARGES

SIDE EFFECTS LEAD TO ER VISITS

Study finds 12 per cent of patients rushed to VGH have adverse reaction to medications

June 3, 2008

"12% of patients rushed to Vancouver General Hospital have adverse reactions to medications."

Zed et al, *Can Med Assoc J*, 2008

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THE NEWSPAPER'S VIEW

Medication-related hospital stays largely a preventable problem

It's bad enough that many people have to wait a long time to be seen by an emergency room doctor or to be admitted to hospital.

It's worse if the holdup is caused, in part, by doctors looking after people who should never have ended up in the hospital in the first place.

Yet as a study in the current issue of the *Canadian Medical Association Journal* has found, many emergency room and hospital patients are being treated for medication-related complaints, and many of those complaints would not occur if medication were prescribed properly and if patients took their meds as directed.

The study's authors considered a random sample of 1,017 patients who presented themselves at Vancouver General Hospital's emergency department between March and June 2006. Of the 1,017 visits, experts determined that 122 (12 per cent) involved medication-related complaints.

Of those 122 problems, 83 (68 per cent) were determined to be preventable, meaning they were the result of the patient being prescribed inappropriate drugs or dosages, not taking them as directed, lack of laboratory monitoring, or dispensing or administration errors.

So a significant number of emergency room patients should never have had to enter the ER in the first place. But that's not the worst of it: 37 per cent of patients with drug-related complaints were admitted to hospital, compared with just 21 per cent of those with non-drug problems. Worse are cluttered with people who wouldn't be there if their drugs were prescribed and taken properly. That places a significant, unnecessary burden on the health care system, and on patients and their families, who must endure stressful emergency room visits and hospital stays.

This also places an onus on both health care providers and consumers to curtail these unnecessary visits. The provincial government is planning an electronic record-keeping system that will improve communication among doctors, pharmacists and other health care providers, and provide information about the best drugs to prescribe, drug interactions and proper dosages.

But doctors and pharmacists must also improve communication with patients, specifically regarding the importance of taking medication as prescribed and the consequences of failing to do so. The current method of handing out a pamphlet at the pharmacy is clearly inadequate.

Further, since patients taking multiple drugs are at greater risk of developing drug-related problems, physicians need to consider whether medication is even necessary, or whether an alternative to drugs might be better.

Finally, patients need to take charge of their health by following their doctors' and pharmacists' advice and also by alerting health care providers to any problems they're having with their medications.

This won't eliminate all drug-related hospital visits, but it could help a

June 5, 2008

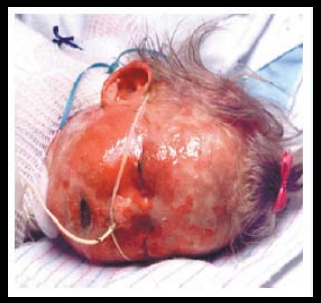
Health Canada

Canada

50% of newly approved therapeutic health products have ***serious ADRs*****,** discovered only after the product is on the market

(Health Canada, 2007)

ADRs in Children



Increased Risk of Severe ADRs in Children

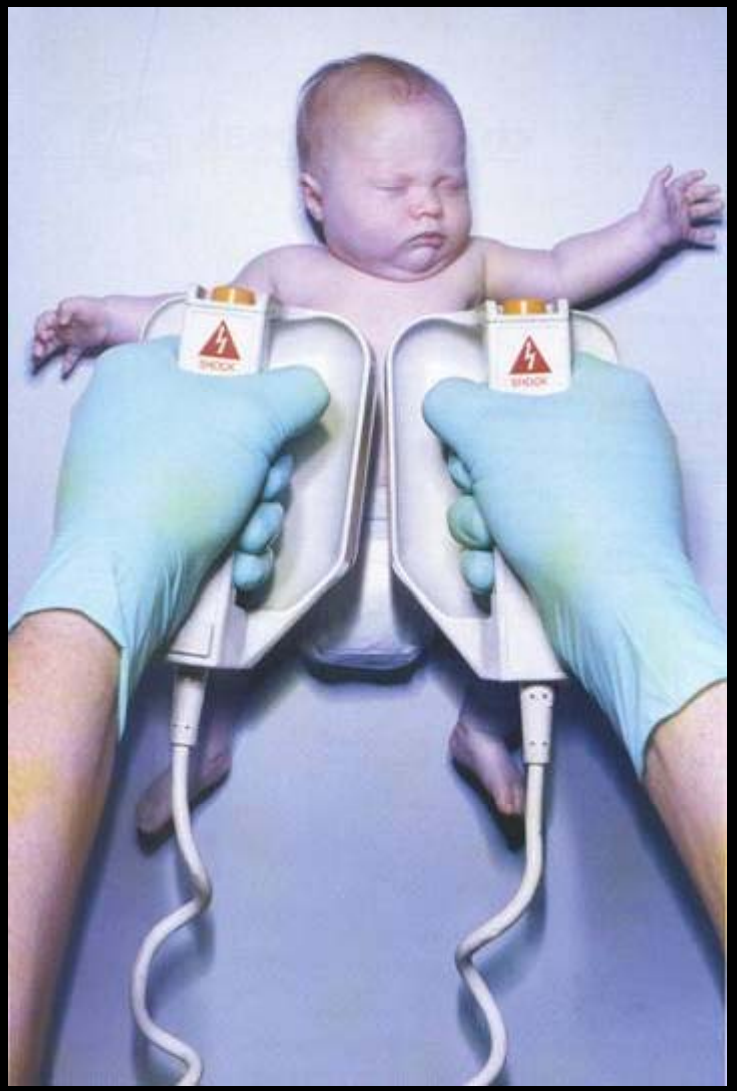
- 11-15% of hospitalized children have an ADR[1-3]
- ADRs cause 22% of admissions in pediatric cancer patients[4]
- 30% of ADRs in hospitalized children are severe causing long-term disability or death[4]
- 26,000 children die each year from ADRs in USA[5]
- Gross lack of knowledge about ADRs in children

1. Gonzalez-Martin *et al*. *Int J Clin Pharmacol Ther* 1998
2. Martinez-Mir *et al*., *Br J Clin Pharmacol*, 1999
3. Takata *et al*, Pediatrics, 2008
4. Mitchell *et al*., *Pediatrics*, 1988
5. Lazarou *et al*, *JAMA*, 1998

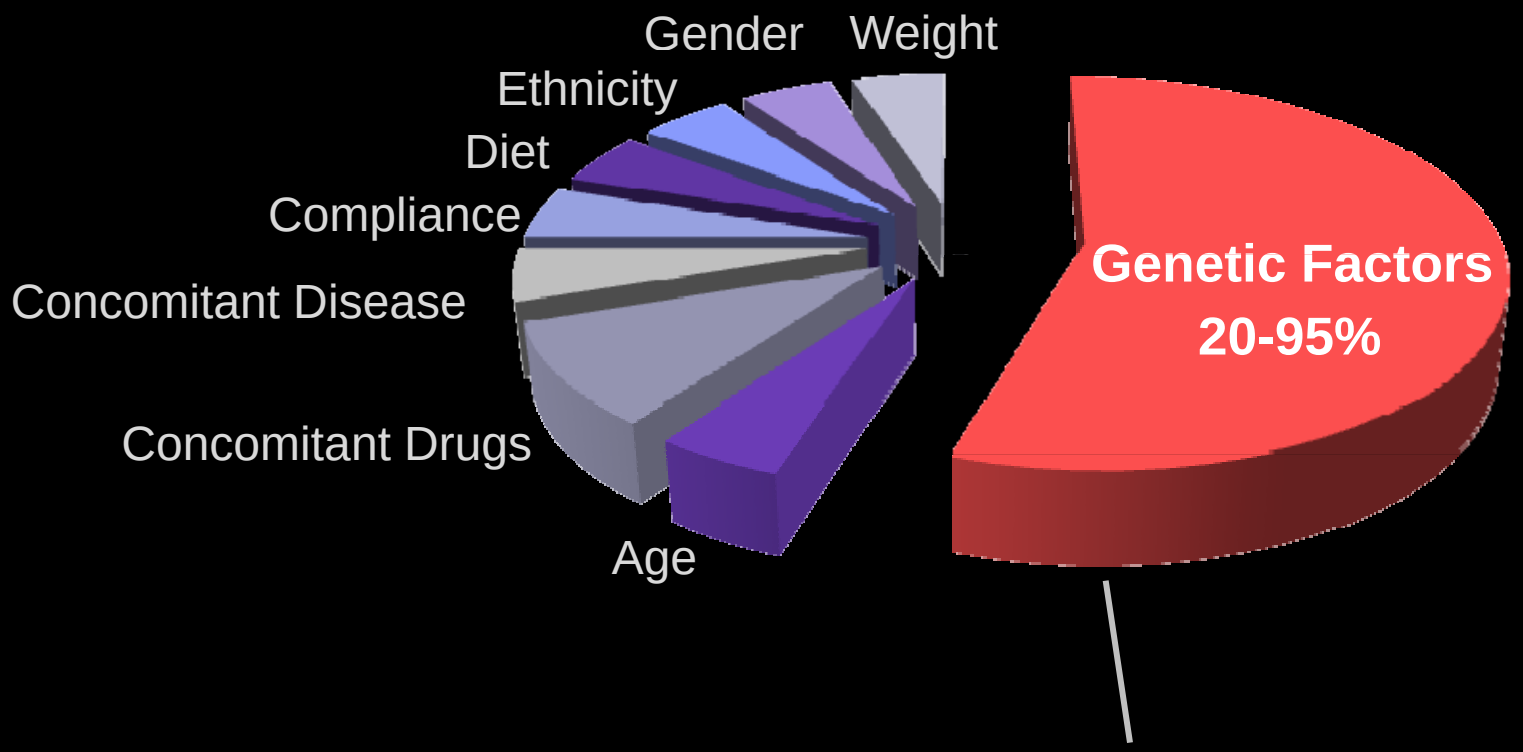
We Can’t Treat Children Like Adults

Increased Risk of Severe ADRs in Children

- >75% of approved drugs used in children are untested in pediatric populations
- Young children cannot evaluate or express their own response to medications
- Pediatric dosage forms not available
- Children metabolize drugs differently than adults



Factors Contributing to Variability in Drug Response



Patient genotype is currently an unknown factor in the prescribing of medicines

How Can The Causes of Variability be Unraveled?

The Canadian Pharmacogenomics Network for Drug Safety

Hypothesis

- Genetic polymorphisms in drug metabolism genes underlie a significant portion of concentration-dependent ADRs in children.

Goal

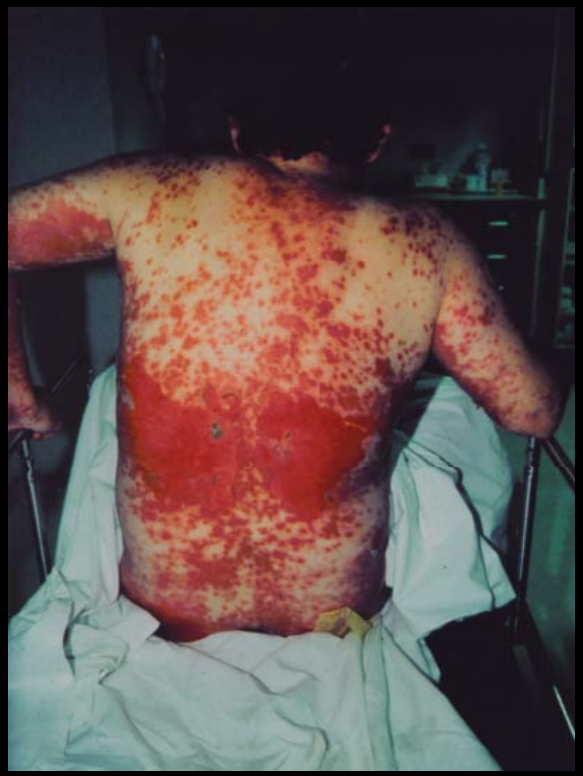
- To develop genotype-based dosing guidelines to predict safety and avoid severe ADRs in children.

Goal is to predict safety and avoid potential complications, not to make effective drugs difficult to obtain for patients

ADR Surveillance

Over 95% of ADRs are not reported

2 studies identified patients being treated for drug-induced T.E.N. in burn units

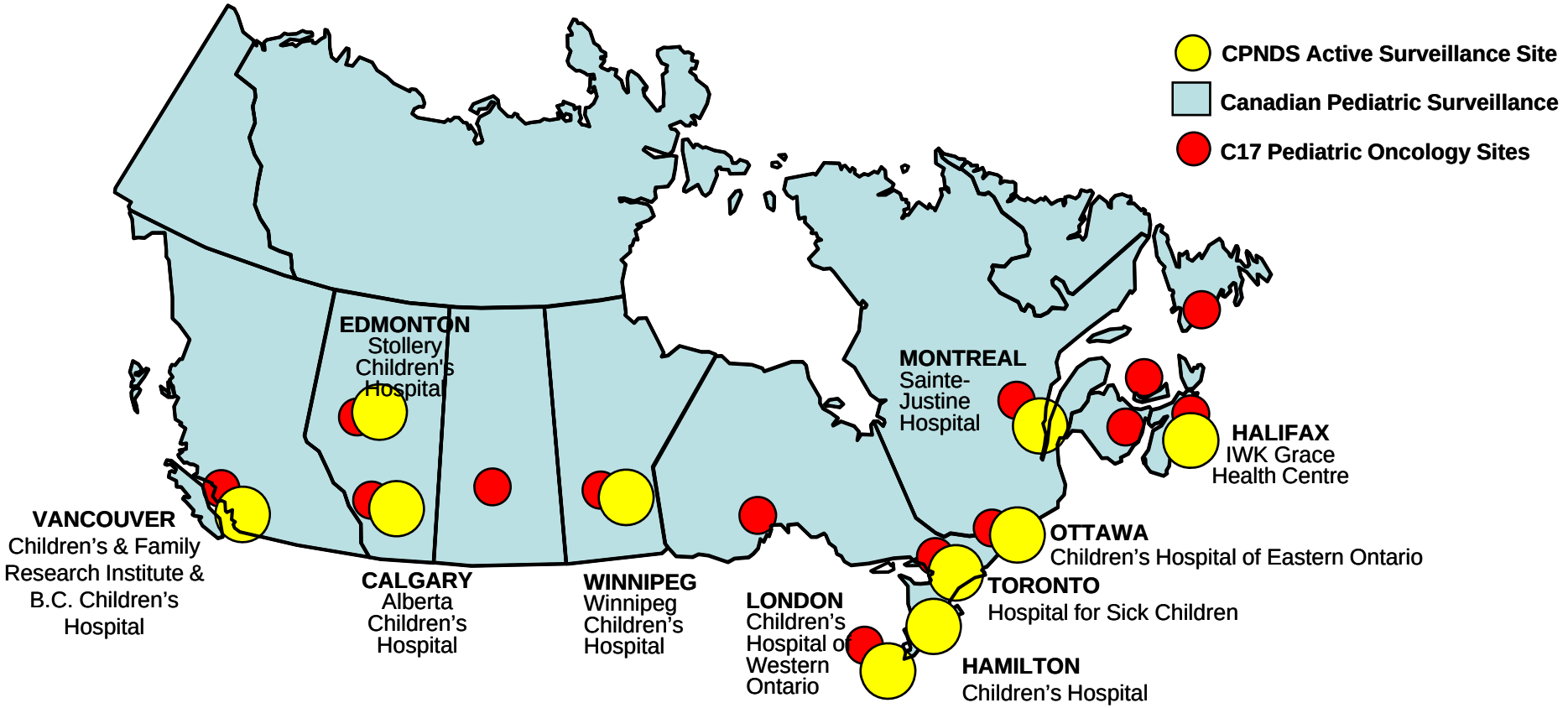


Q: What % of these ADRs were reported ?

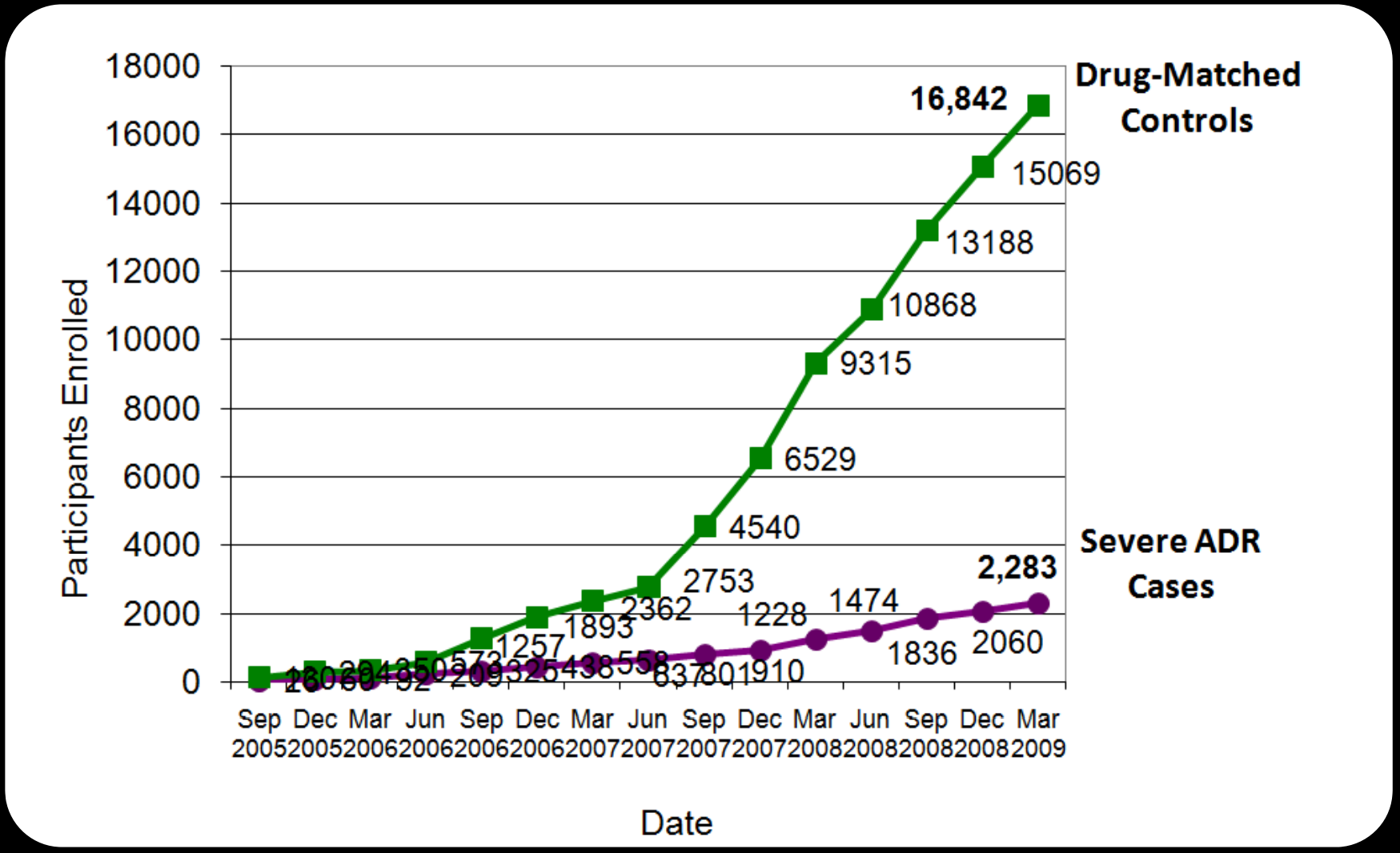
4% ADR Reporting Mittman et al., Drug Safety 2004;27(7):477-87.

2.5% ADR Reporting Rzany et al., J Clin Epidemiol 1996;49(7):769-73

Canadian Pharmacogenomics Network for Drug Safety



Recruitment of ADR Cases and Drug-Matched Controls



Genomic Analyses

Association Study

Patients with Disease

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ACGTAGATATTTAAAGGGCGTGTGCACGTGACGTACACACAGTACTTTT
ACGTATATATTTGAAGGGCGTGTGGACGTGACGTACACACAGTACTATT
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ACGTAGATATTTGAAGGGCGTGTGGACGTGACGTACACACAGAACTATT
ACGTATATATTTAAAGGGCGTGTGGACGTGACGTACACACAGTACTTTT

Control Unaffected Patients

ACGTATATATTTAAAGGGCGTGTGGACGTGACGTACACACAGAACTTTT
ACGTAGATATTTGAAGGGCGTGTGCACGTGACGTACACACAGAACTATT
ACGTATATATTTAAAGGGCGTGTGGACGTGACGTACACACAGAACTTTT
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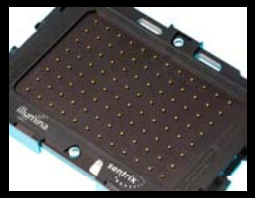
ACGTATATATTTAAAGGGCGTGTGGACGTGACGTACACACAGAACTATT
ACGTAGATATTTGAAGGGCGTGTGCACGTGACGTACACACAGAACTTTT

Odds Ratio = 16
P value = 0.02

- **Genome Canada's** GATC Project supported the acquisition of the Illumina 500GX platform at the CMMT

Centre for Molecular Medicine & Therapeutics
Vancouver, B.C.



Illumina Sentrix™ Array Matrix

ADME/Tox Genes SNP Arrays

Gene Classification	Examples
Phase I Metabolizing Enzymes	CYP1A1, CYP2B6, ALDH2
Phase II Metabolizing Enzymes	UGT2B7, GSTM1, NAT1, COMT
Receptors / Drug Targets	VDR, PPARG, CETP
Transporters	ABCB1, ABCC1, ABCC2
Transcription factors	HNF4A, STAT3, NR1I2
Immunity	HLA variants
Ion Channels	SCN5A, KCNH2, KCNQ1
Others	EPHX1, FMO1, PTGS1

Current: 3072 SNP array

1536 HapMap derived haplotype tag SNPs

1536 Altered enzyme activity common non-synonymous, literature validated rare non-synonymous, synonymous coding SNPs

Other options:

6144 to 1.1 million SNP arrays

SNP Genotyping

DNA
(blood, saliva, buccal)

DNA Purification Robots

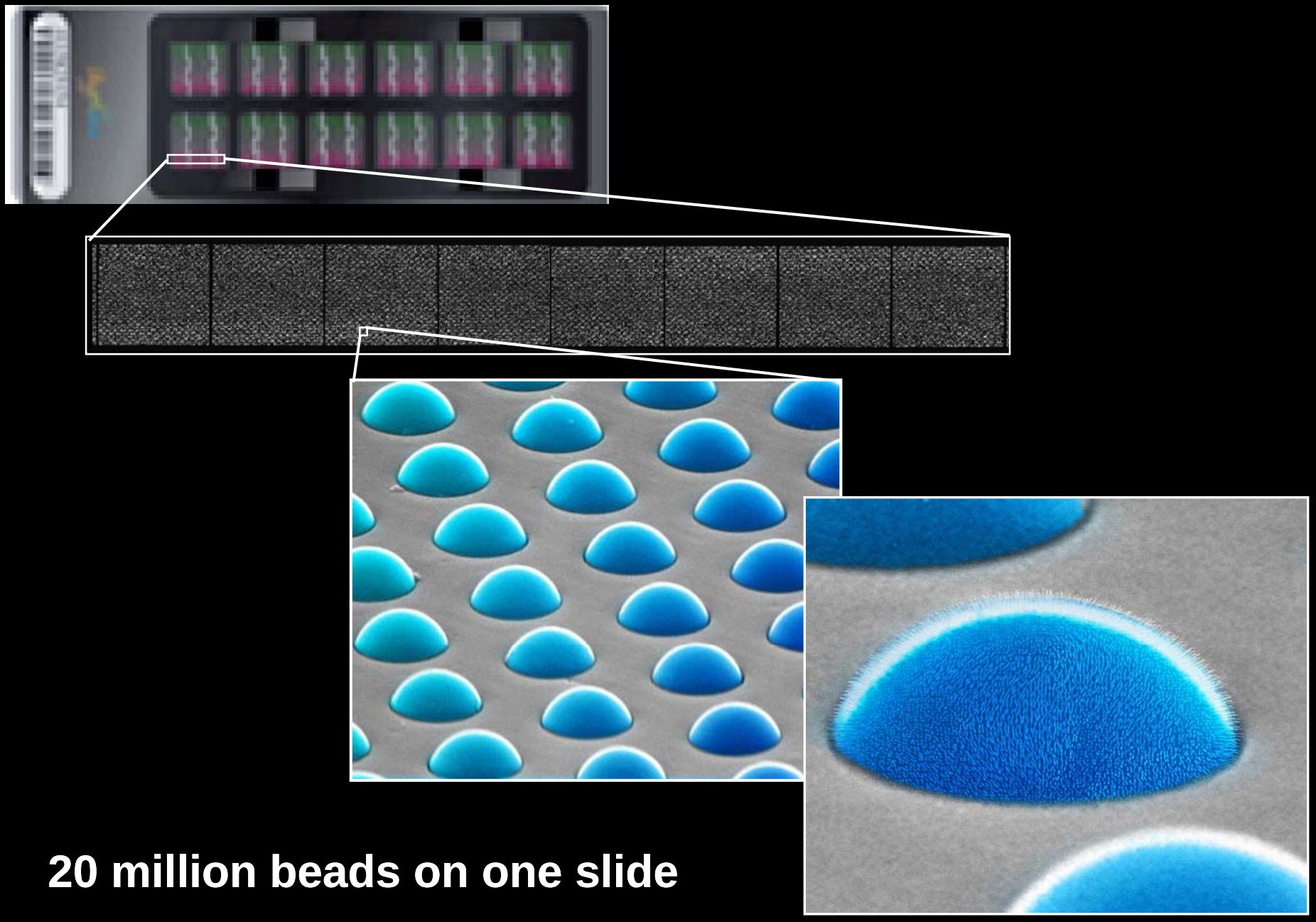
2D Laser Etched
Bar-coded Samples

Long Term
Storage -80°C

Illumina BeadXpress
1-384 tests per sample

Illumina BeadStation
384-1.2 million test per sample

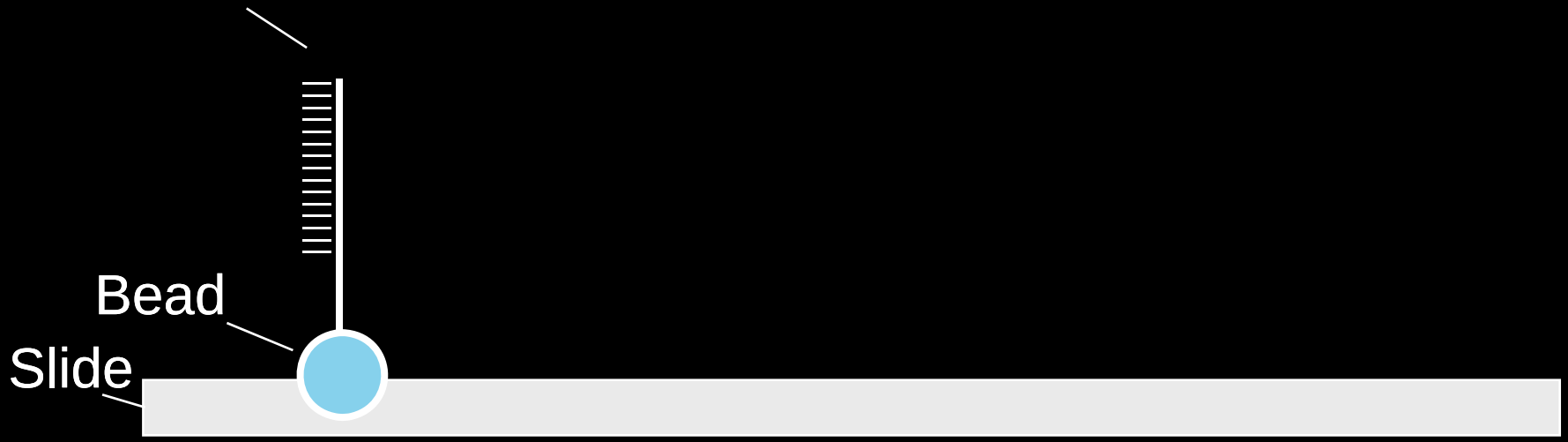
Illumina SNP Genotyping



20 million beads on one slide

Illumina SNP Genotyping

DNA target capture probe affixed to bead: Complementary to SNP region (50 bp)



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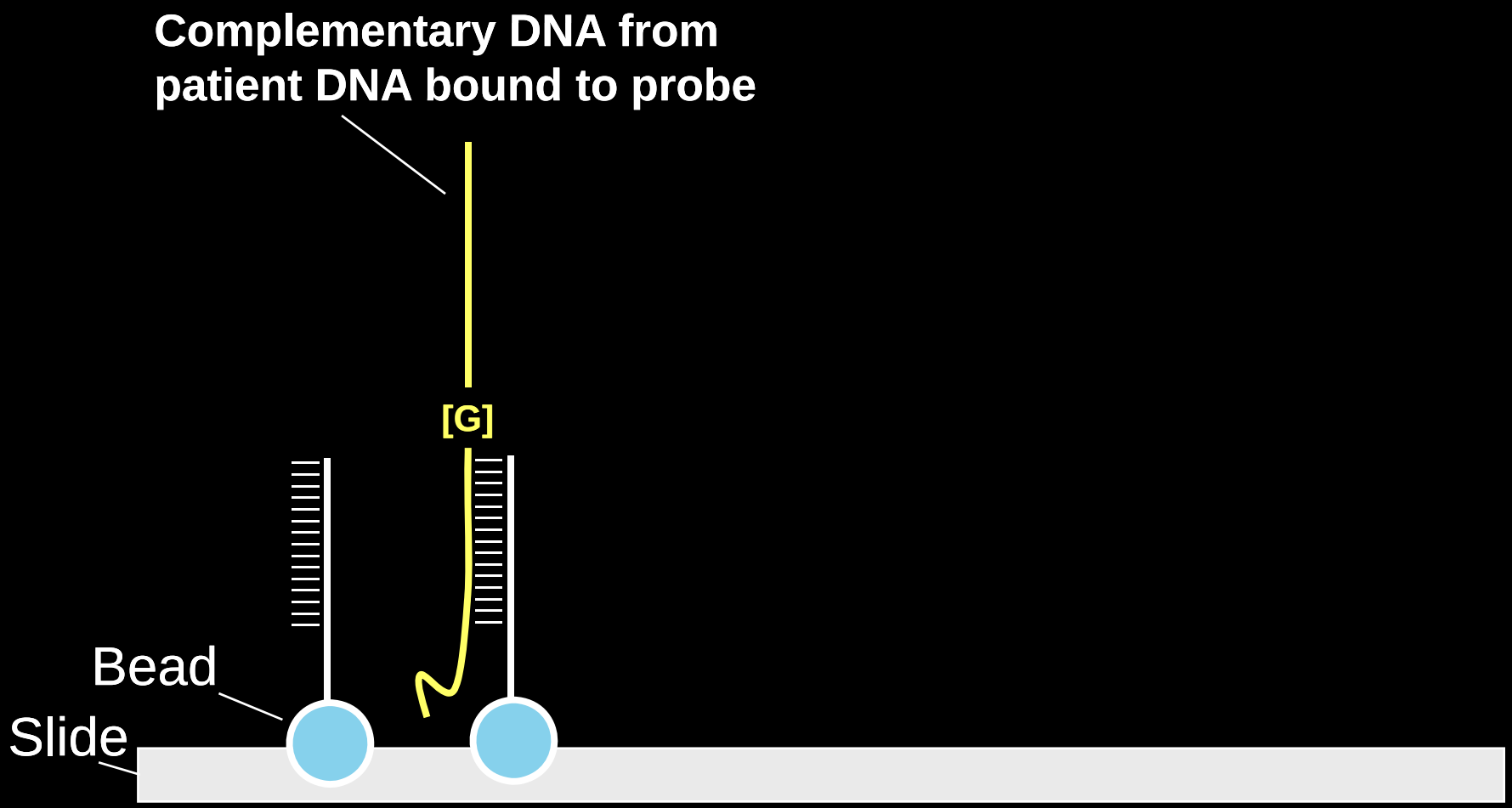

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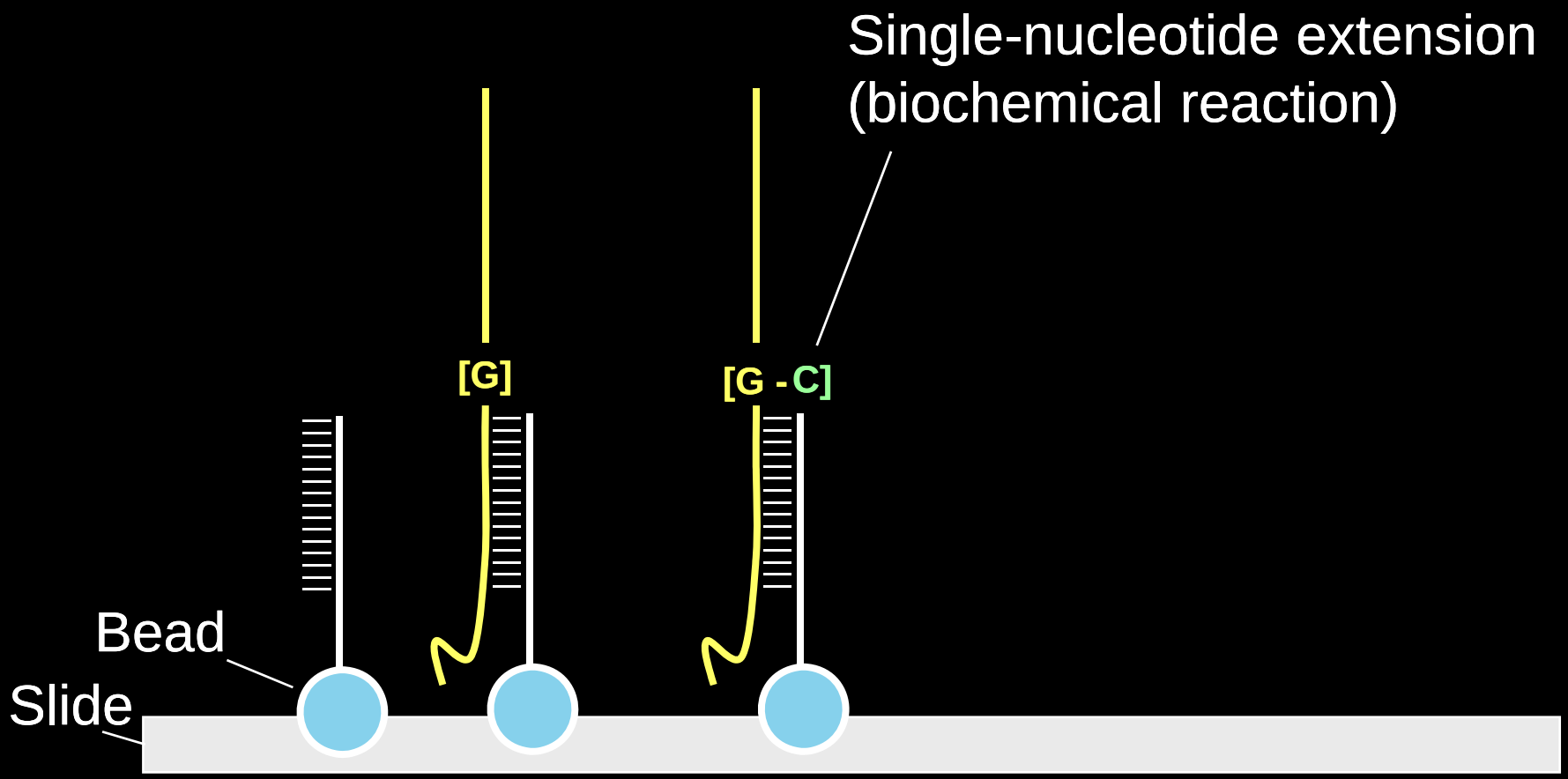

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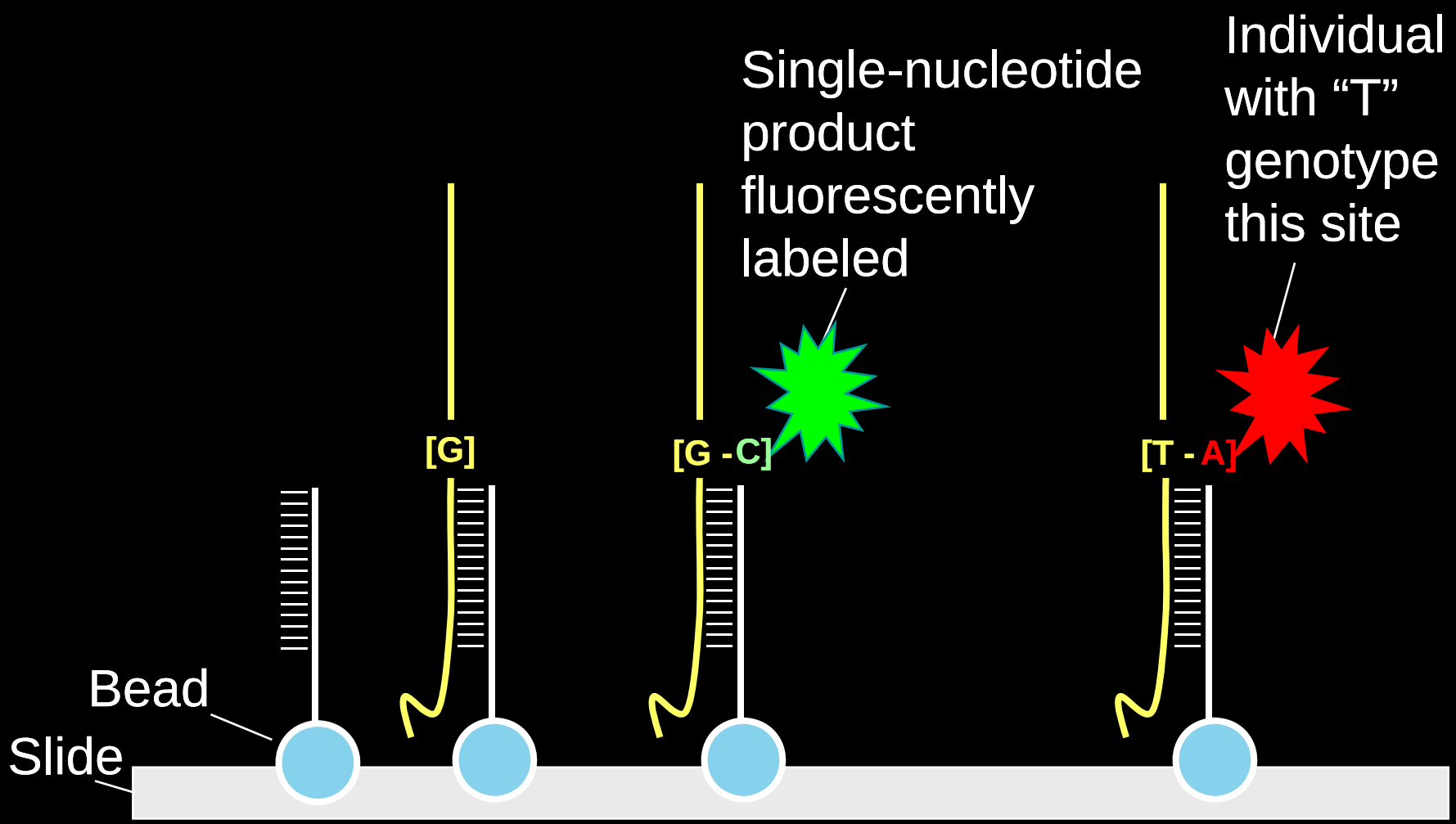

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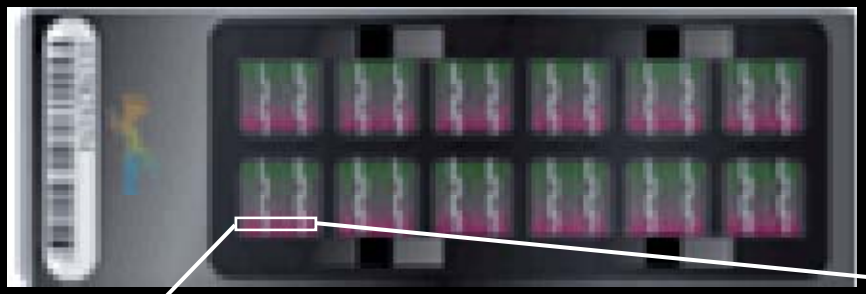
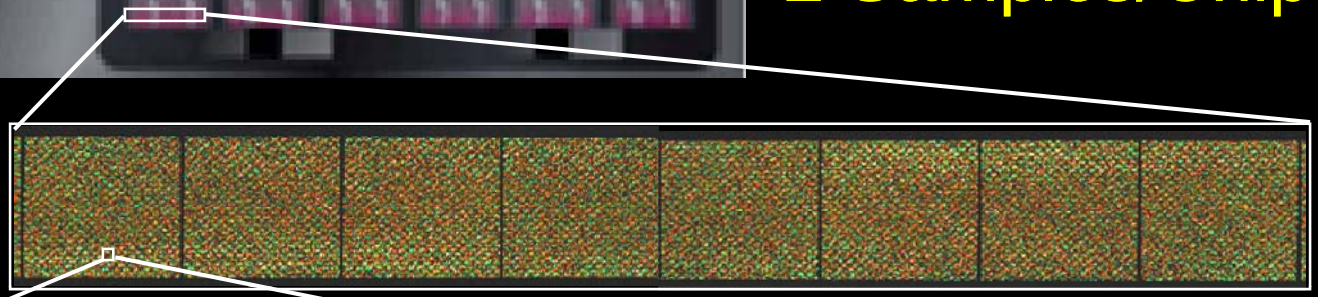
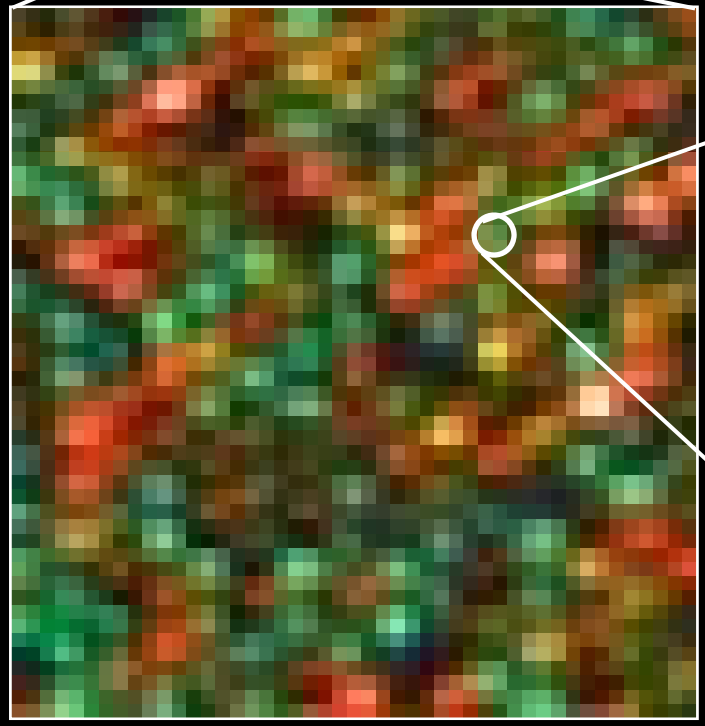
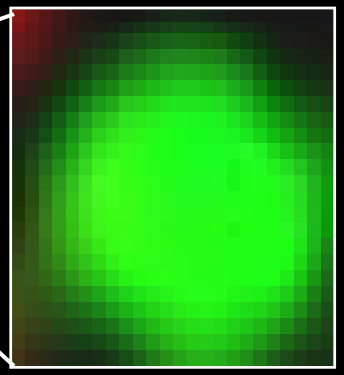
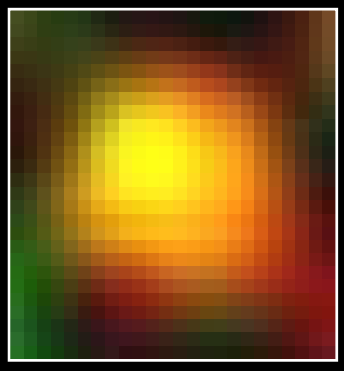


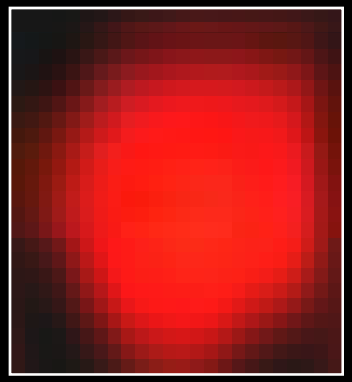
1.2M Chip (1.2 million SNPs)
2 Samples/Chip









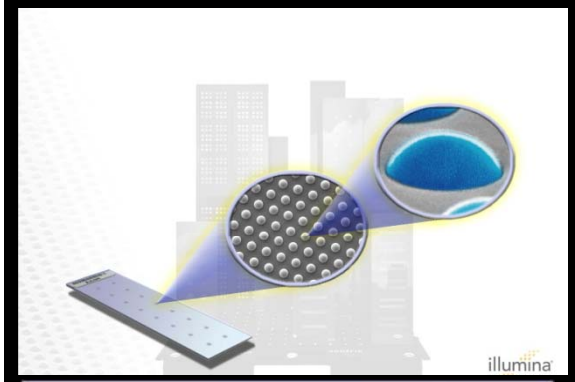


[T/T] [T/G] [G/G]

Examples of SNP Genotyping Formats

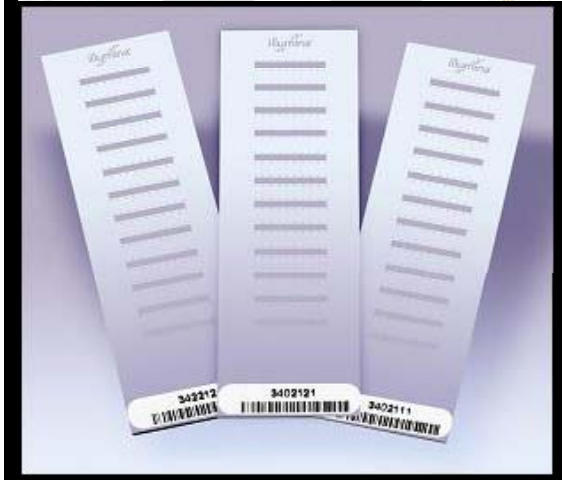
1. Custom SNP Panels

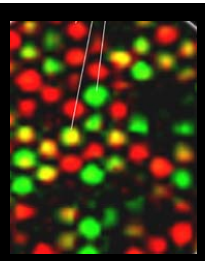
- 1 to 200,000 SNPs/assay



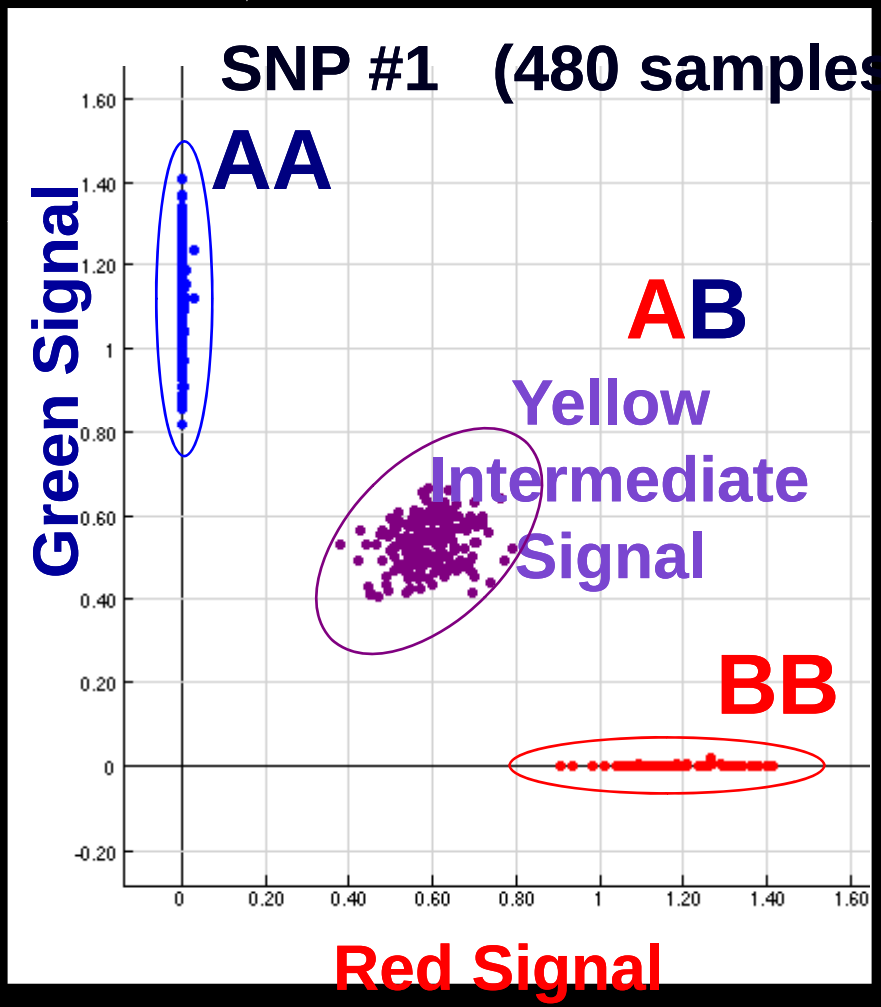
2. Human Genome-wide SNP panels

- 300,000 SNPs Genome-wide
  - 12 samples/chip
  - Highly cost-effective
- 660,000 SNPs Genome-wide
- 1.2 Million SNPs Genome wide





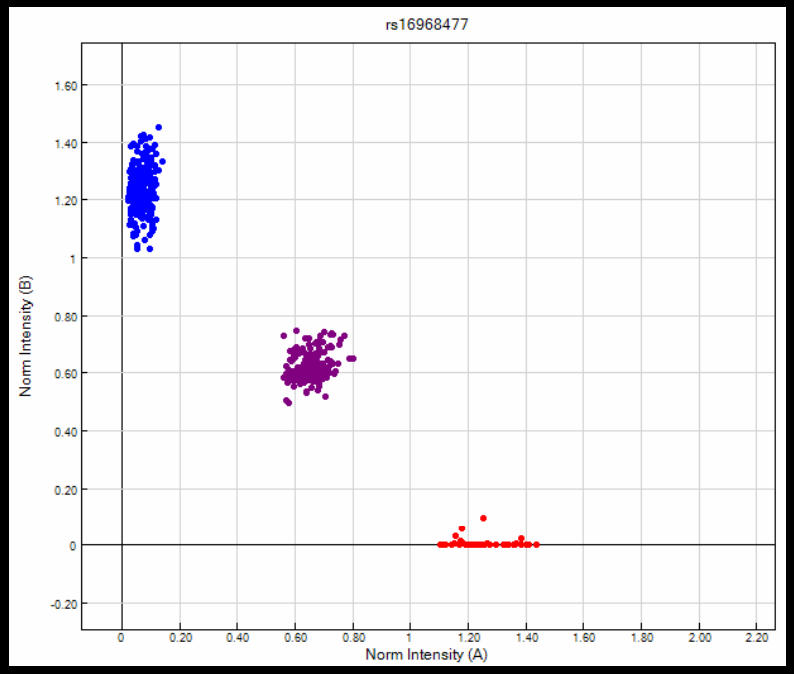
Raw
Fluorescence
Intensity Data

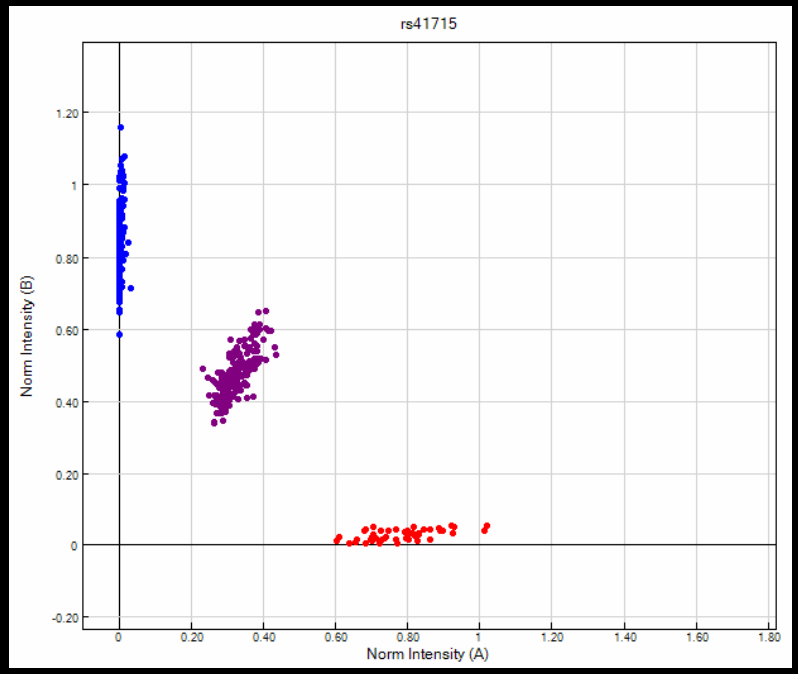


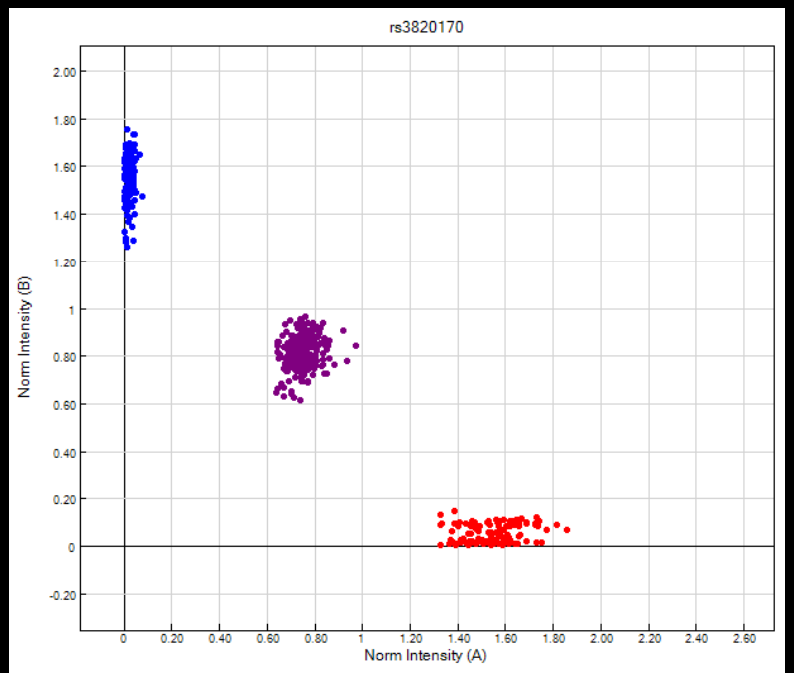
Genotype Text
Output

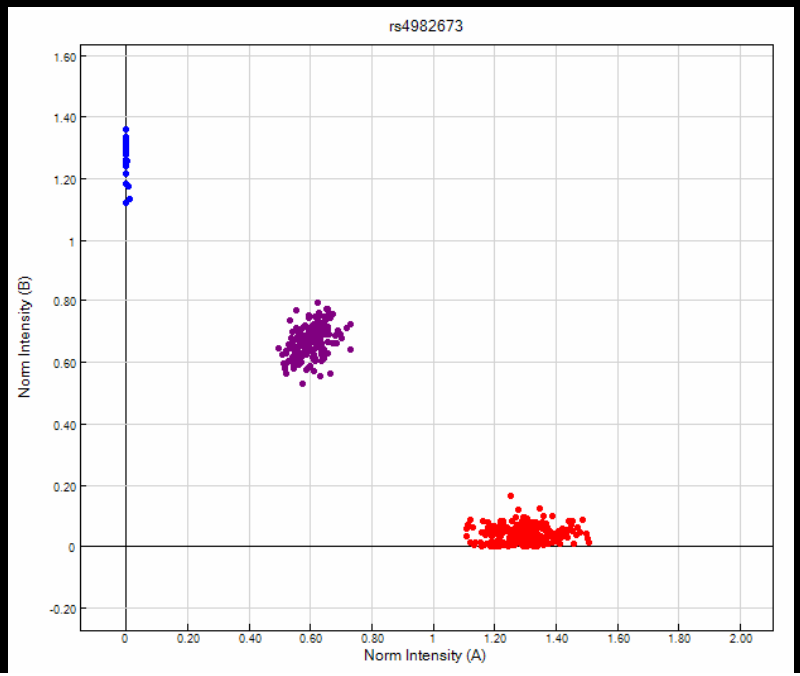
SNP 1 AA
SNP 2 TT
SNP 3 GG
SNP 4 GC

Raw SNP Data (n = 480)

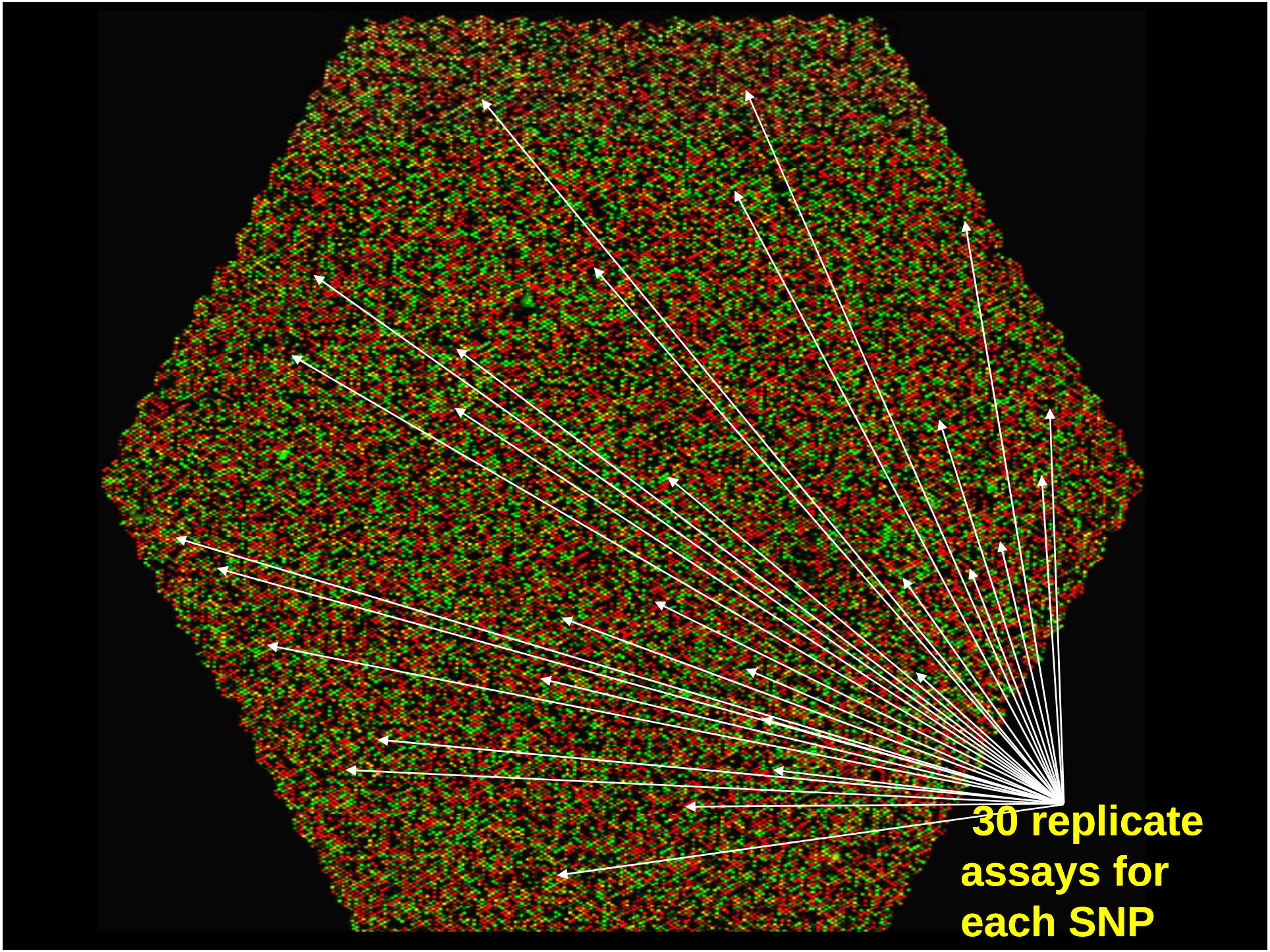








- **SNP assay conversion rates for tag SNPs: 90-96%**
- **High Genotype Call Rates: >99%**
- **High Reproducibility: >99.99%**
  - 16 miscalls out of 178,860 genotype calls (58 patient DNA replicates)
  - 0 miscalls out of 50,688 genotype calls (16 control DNA replicates)


30 replicate
assays for
each SNP

Illumina BeadXpress (Veracode) SNP Genotyping

- 384 samples x 384 SNPs
- SNP Conversion Rate: 95.05% (368/384)
  (# of SNPs that could be assayed)
- Average Call Rate: 99.32% (min. 93%, max. 99.7%)

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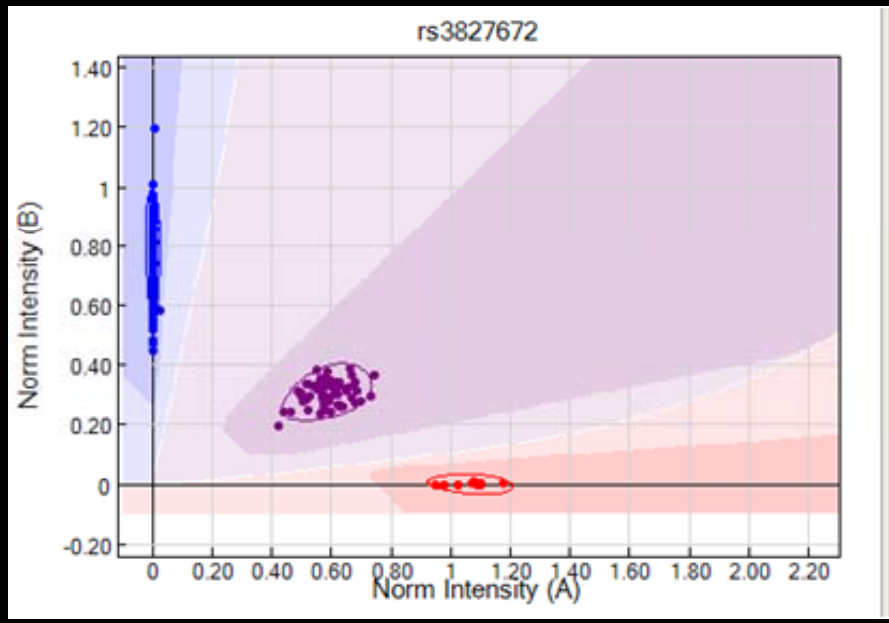
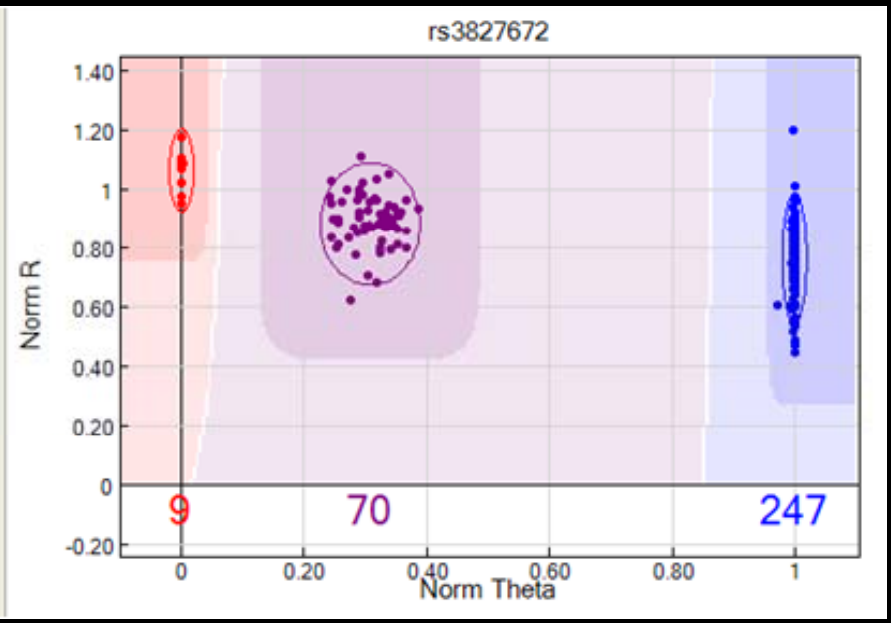
Average SNP: GenCall Score = 0.86

Cartesian View



Polar View



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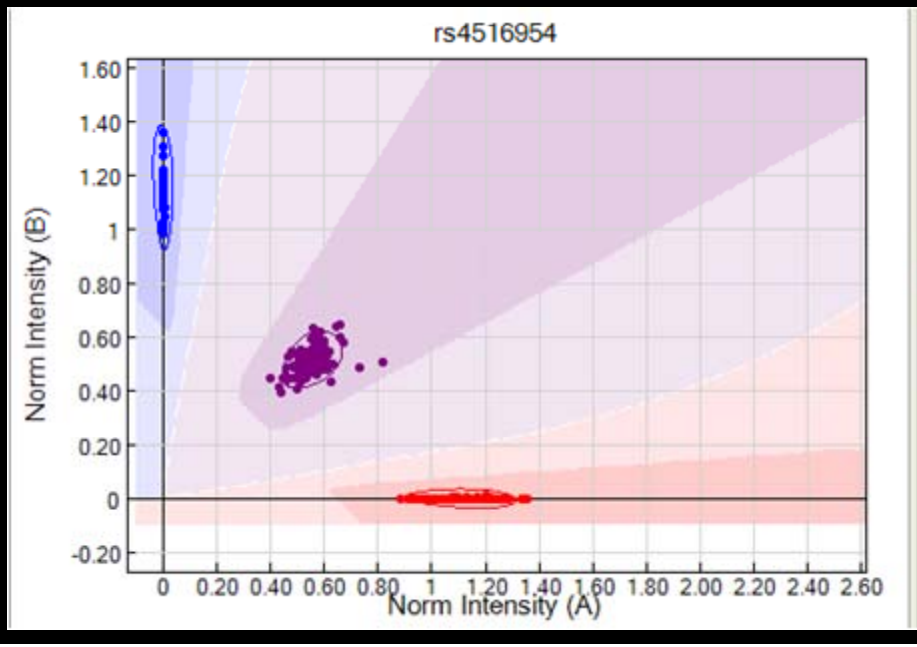
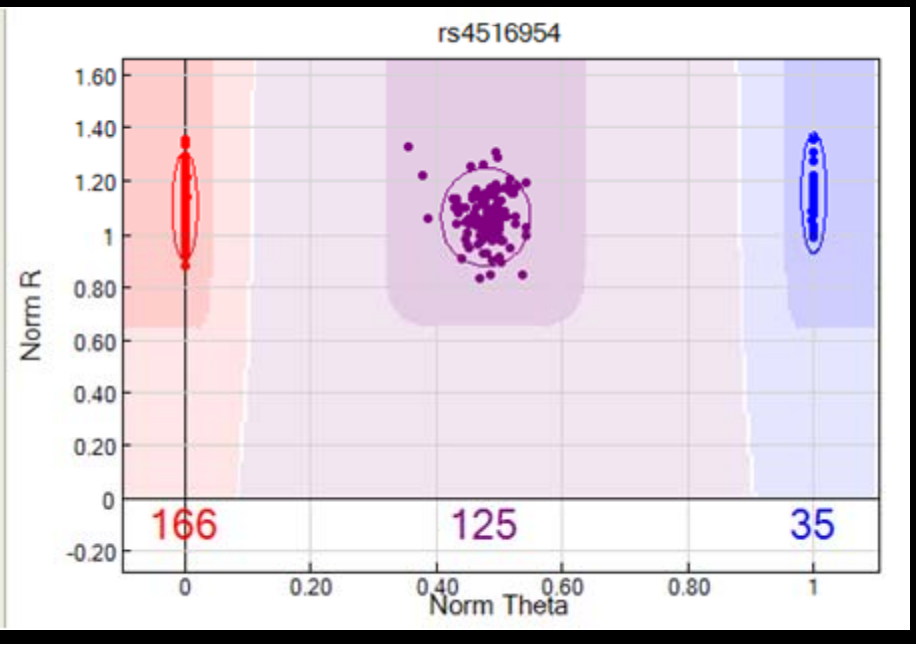
Best SNP: GenCall Score = 0.969

Cartesian View



Polar View



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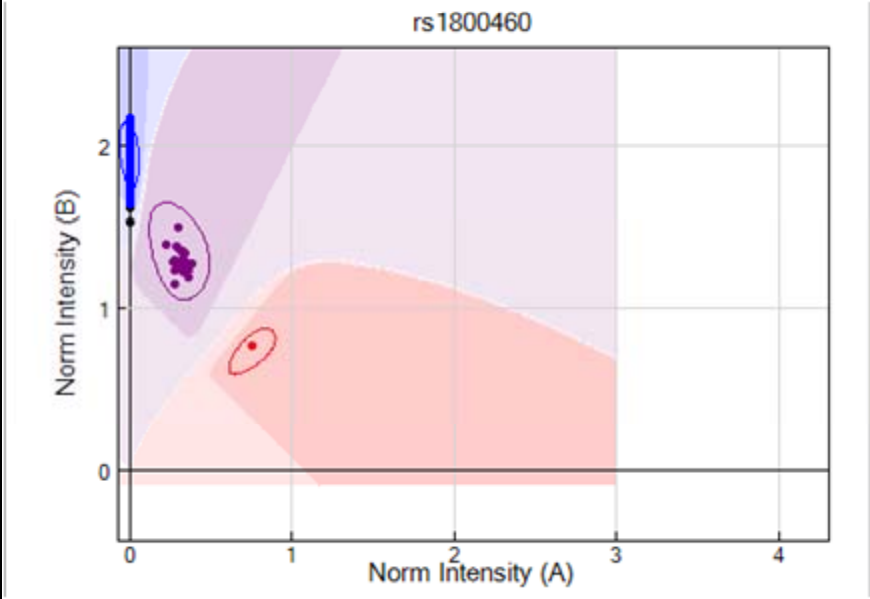
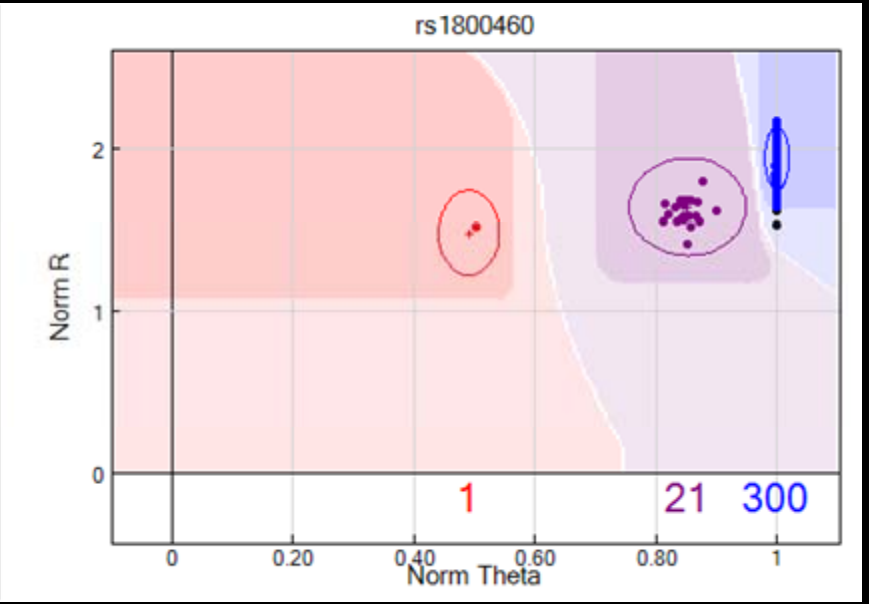
- **SNP Conversion Rate: 95.05% (368/384)**
  (# of SNPs that could be assayed)
- **Average Call Rate: 99.32% (min. 93%, max. 99.7%)**

Worst SNP: GenCall Score = < 0.30

Cartesian View



Polar View



CPNDS Priority ADR Targets

In Progress:

- **Codeine-induced infant mortality**
- **Cisplatin-induced deafness**
- **Anthracycline-induced cardiotoxicity**
- Life-threatening skin reactions
- Vincristine-induced neuropathy
- Statin-induced muscle damage
- Interferon-β toxicity
- Warfarin-induced bleeding/thrombosis

Codeine

The American Academy of Pediatrics and major authoritative texts list codeine as compatible with breastfeeding

– Briggs et al., 2005; Pediatrics, 2001

Codeine-Induced Adverse Reaction

Case Report

- A new mother was given Tylenol #3 for obstetric pain relief
  - Given a standard dose (60 mg every 12 hours)
- Mother complained of significant drowsiness
  - Codeine dose cut in half (30 mg every 12 hours)
- Infant showed poor feeding
- Infant died on day 13 due to respiratory failure

Follow-up Analysis:

- Maternal milk from last day of the baby's life contained morphine at 10-20x higher levels than expected (87 ng/ml)
- Infant's blood contained lethal levels of morphine (70 ng/ml)

Identified genetic variants associated with a lethal adverse reaction to codeine in newborns

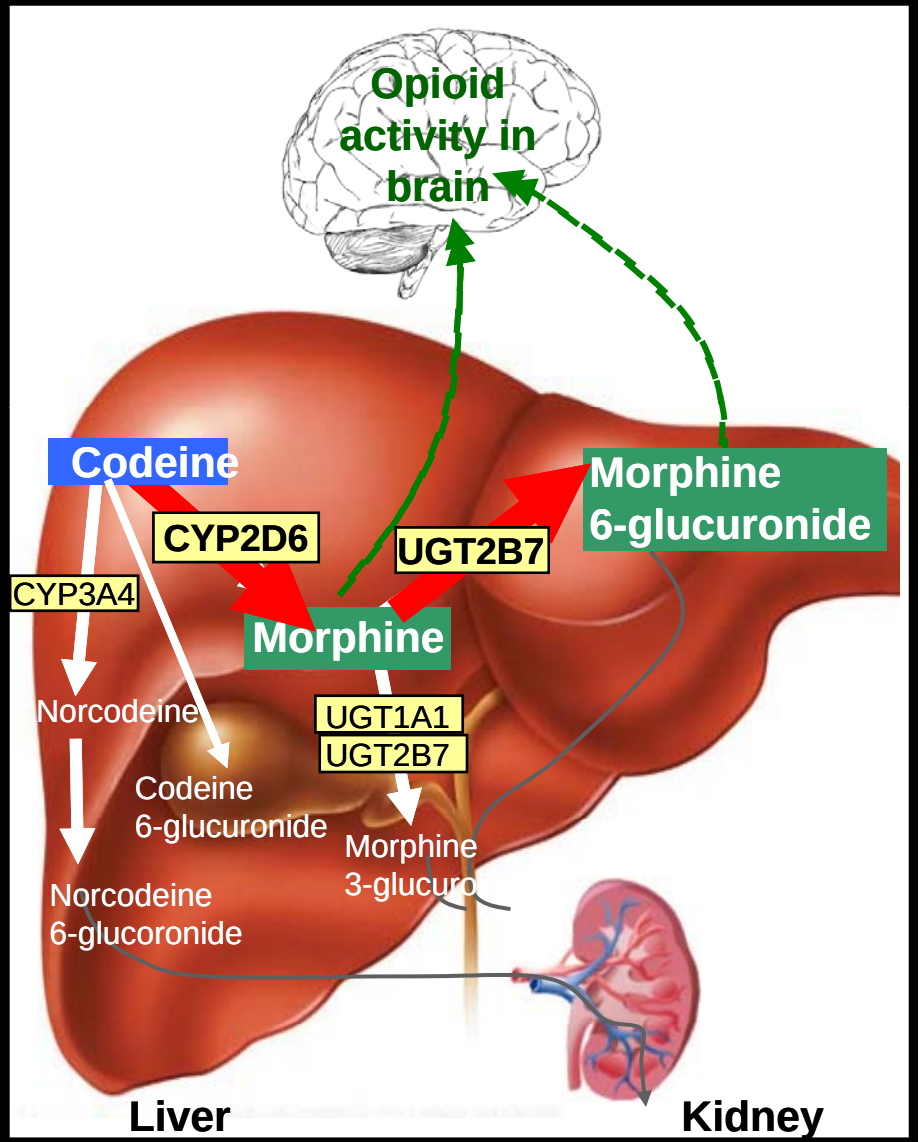
Mother's Genotype:

CYP2D6 gene duplication

UGT2B7*2/*2

Outcome:

- Accumulation of morphine in breast milk (10-20x more than normal)
- Breast milk fed to infant
- Infant died at 13 days of age
- Lethal levels of morphine accumulated in the infant causing CNS depression, respiratory failure, and death



Completed Codeine Case-Control Validation Study

nature publishing group ARTICLES

Pharmacogenetics of Neonatal Opioid Toxicity Following Maternal Use of Codeine During Breastfeeding: A Case–Control Study

P Madadi[1,2], CJD Ross[3], MR Hayden[3], BC Carleton[4], A Gaedigk[5], JS Leeder[5] and G Koren[1,2,6]

A large number of women receive codeine for obstetric pain while breastfeeding. Following a case of fatal opioid poisoning in a breastfed neonate whose codeine prescribed mother was a CYP2D6 ultrarapid metabolizer (UM), we examined characteristics of mothers and infants with or without signs of central nervous system (CNS) depression following codeine exposure while breastfeeding in a case–control study. Mothers of symptomatic infants ($n = 17$) consumed a mean 59% higher codeine dose than mothers of asymptomatic infants ($n = 55$) (1.62 (0.79) mg/kg/day vs. 1.02 (0.54) mg/kg/day; $P = 0.004$). There was 71% concordance between maternal and neonatal CNS depression. Two mothers whose infants exhibited severe neonatal toxicity were CYP2D6 UMs and of the UGT2B7*2/*2 genotype. There may be a dose–response relationship between maternal codeine use and neonatal toxicity, and strong concordance between maternal-infant CNS depressive symptoms. Breastfed infants of mothers who are CYP2D6 UMs combined with the UGT2B7*2/*2 are at increased risk of potentially life-threatening CNS depression.

May 10, 2006

FDA drug label change and public health advisories

Aug 17, 2007

Health Canada Public Advisory

Aug. 21, 2008

Estimated 1846 newborn infants are at risk for this codeine ADR each year in Canada

(340,000 births, 73% breastfed, 52% mothers receive codeine post-childbirth,1.4% risk genotype)

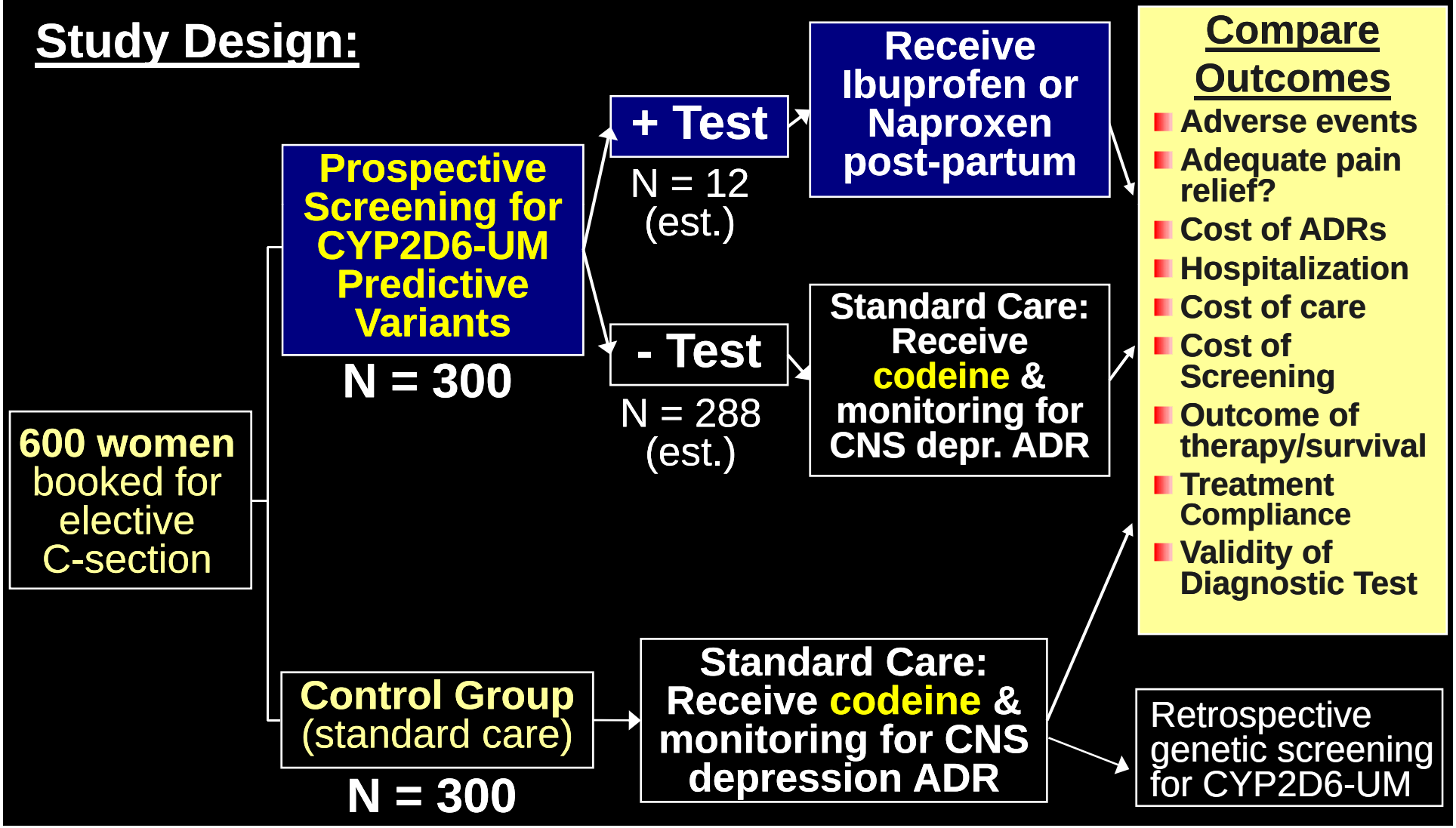
Additional Cases of Infant Toxicity from Codeine from Literature

- 35 reports of breastfeeding infants with ADRs to codeine, including:
  - Unexplained severe drowsiness
  - Apnea
  - Bradycardia
  - Cyanosis

Currently Performing Randomized Controlled Trial

- **Prospective study to test the assess the benefit of a diagnostic test to prevent codeine ADRs in infants**

Study Design:



ADRs in Chemotherapy

Cancer Survival has Improved, but Survivors often Left with Lifelong Consequences of Severe ADRs

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April 10, 2008

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82% of children beat cancer

Survivors are often left with lifelong health consequences

By KRISTEN THOMPSON

April 10, 2008 02:24

More children are surviving cancer than ever before, according to statistics released yesterday by the Canadian Cancer Society. But experts are finding that survival often carries lifelong health consequences.

Seven-year-old Casey Wright, from Maple Ridge, is among the 82 per cent of children diagnosed with cancer who survive thanks to progress in treatments — an 11 per cent increase in the past 15 years.

But he also represents the two-thirds of survivors who have to live with chronic or late-occurring health effects.

RAFE ARNOTT/METRO VANCOUVER

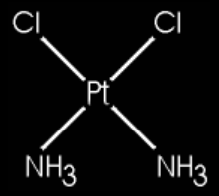
Casey Wright, 7, hugs his sister Jemma, 9, during lunch hour yesterday at Maple Ridge elementary as their mother, Kim, discusses his recovery from a malignant brain tumour.

Pediatric Oncology:

- 1 in 750 young adults are survivors of childhood cancer
  - 75% of cancer survivors suffered at least 1 ADR
  - **40%** of cancer survivors have had a severe ADR (life-threatening, or disabling)
  - 25% of cancer survivors suffer 5 or more ADRs

Geenan et al, *JAMA*, 2007

Cisplatin-Induced Deafness



Cisplatin

- A highly effective anti-tumor agent
- Treatment of solid tumours including ovarian, lung, bladder, head and neck
- **In children: treatment of CNS tumors, hepatoblastoma, neuroblastoma, osteosarcoma**
- >**1,000,000 patients** receive each year (N. America & Europe)

Case Studies

Case 1

- 14 yrs old
- Osteosarcoma of Right proximal tibia
- Diagnosed Nov 2000
- Chemotherapy:
  - Cisplatin
  - Doxorubicin
  - Methotrexate
- Alive and Well

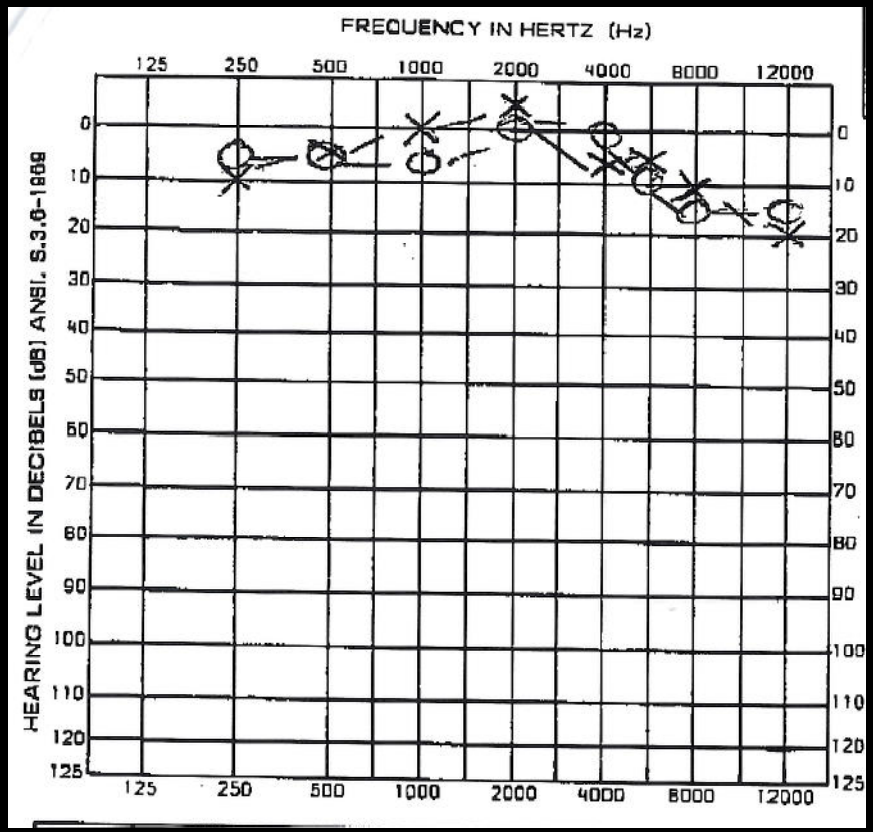
Case 2

- 12 yrs old
- Osteosarcoma of Right Proximal tibia
- Diagnosed Oct 1998
- Chemotherapy:
  - Cisplatin
  - Doxorubicin
  - Methotrexate
- Alive and Well

OVERALL: Cases sound similar
Same tumor, treatment, and cure outcomes

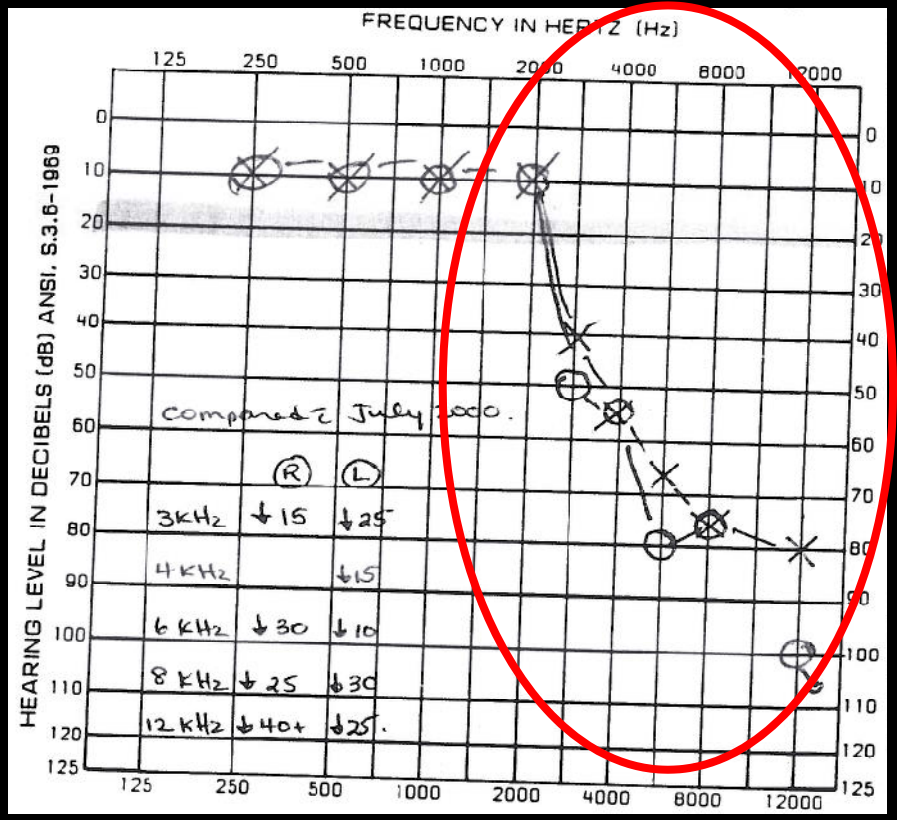
Case 2 Suffered Severe Hearing Loss

Case 1



Normal Hearing Audiogram

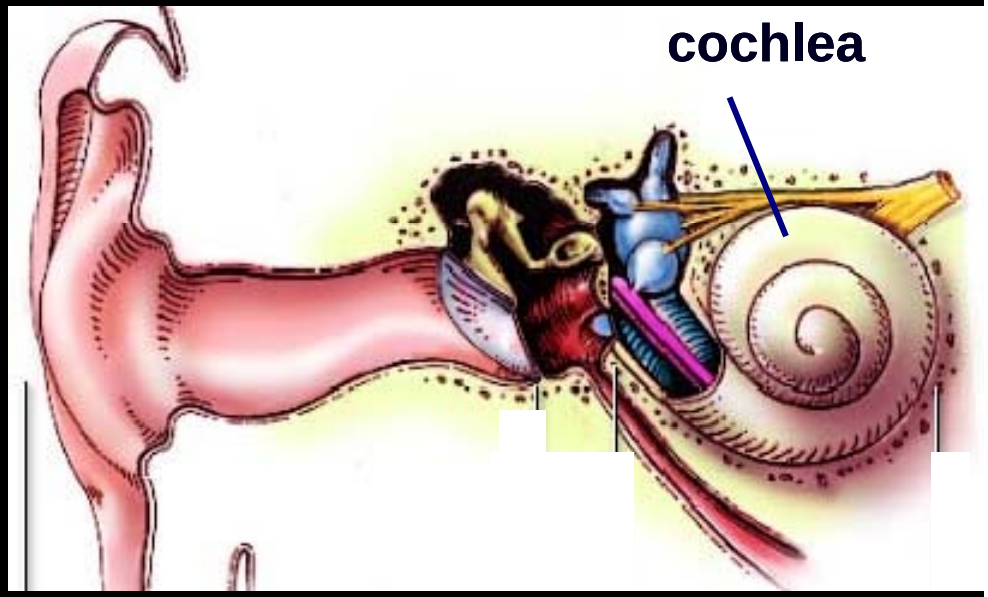
Case 2



Severe Hearing Loss

Cisplatin-Induced Deafness

- Causes permanent hearing loss
  - Bilateral, hair cell degeneration in cochlea
  - Initially high freq. loss (cells with higher metabolic activity)



- 10-38% of adult patients affected

- Increased frequency and severity in children
  - **28-61%** of children 5-14 develop severe hearing loss
  - **38-62%** of children <5 yrs old develop severe hearing loss

Cisplatin-ADR Patient Recruitment

- 162 pediatric patients with hepatoblastoma, brain tumor, germ cell tumours, neuroblastoma, osteosarcoma

Classification of Cisplatin ADR Cases and Controls

Controls

- **Grade 0: Normal Hearing**
  Hearing threshold of 20 dB or less (within normal range) at all frequencies

n = 56

- **Grade 1 Hearing Loss: Mild High Freq. Loss**
  Minimum hearing threshold of 20-25 dB (4000 Hz and above)

ADR Cases

- **Grade 2 Hearing Loss: Moderate High Freq. Loss**
  May require speech therapy or intervention with hearing aid
  Minimum hearing threshold of 25-39 dB (4000 Hz and above)
- **Grade 3 Hearing Loss: Severe Hearing Loss**
  Requires intervention with hearing aid
  Minimum hearing threshold of 25-39 dB (2000 Hz and above)
- **Grade 4 Hearing Loss: Deafness**
  Requires intervention with cochlear implant
  Minimum hearing threshold of 40dB or more (1000Hz and above)

n = 106

Multistage Approach

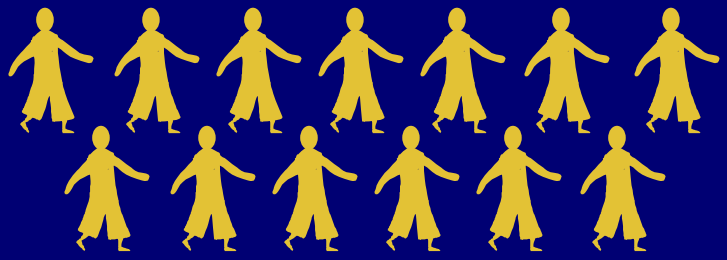
Stage 1: Discovery

N = 55 Vancouver

Genotype full set of SNPs in relatively small population at liberal *p* value

P < 0.01

Stage 2: Replication



N = 107 Canada-wide

Screen second, larger population at more stringent *p* value

P < 0.005

Joel Hirschhorn & Mark Daly, *Nature Reviews*, 2006

What Next?

Patient Predicted to be at High Risk for Cisplatin-Induced Ototoxicity

What is done now without a predictive test:

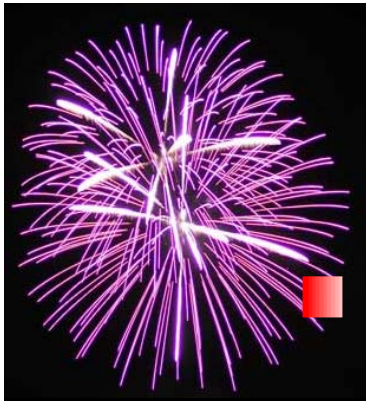
Protocol	Treatment	Ototoxicity	Intervention
Osteosarcoma	Doxorubicin & cisplatin	Grade 2	**Reduce cisplatin 50%**
		Grade 3+	**Discontinue cisplatin**
Brain tumor	Cisplatin, Etoposide, + Vincristine	Grade 2	**Reduce cisplatin 50%**
		Grade 3+	**Discontinue cisplatin**
Osteosarcoma	Doxorubicin + cisplatin	Grade 3+	**Discontinue cisplatin**

What Next?

Patient Predicted to be at High Risk for Cisplatin-Induced Ototoxicity

Predictive testing:

- Alternative drug
- Increase monitoring in high risk patients e.g. patients in rural centres
- Experimental Protective Strategies to prevent cisplatin-ototoxicity
  - Sodium Thiosulfate
  - N-acetylcysteine D-methionine
  - Glutathione ethyl ester



In the Future

- Pharmacogenomics could have profound impact in medicine
- Advances in technology opening the doors to understanding the genetic factors of ADRs
  - Whole Genome Sequencing
  - Routine genotyping of millions of SNP variants
- Lower health care costs:
  - ADRs now exceed the cost of medications in USA/Canada
- Improved safety
  - Safer and More Effective Treatments

Canadian PGx Network for Drug Safety

Pharmacogenomics: Michael Hayden, UBC
Michael Phillips, Montreal
Colin Ross, UBC
Steven Leeder, Univ of Missouri

ADR Surveillance: Bruce Carleton, UBC
Gideon Koren, Univ Toronto
Stuart MacLeod, UBC
Doreen Matsui, UWO

Audiology: Beth Brooks, BC Childrens

Pediatric Oncology: Paul Rogers, BC Childrens
Rod Rassekh, BC Childrens

Pharmacokinetics: Michael Rieder, UWO
David Freeman, UWO

Data Analysis: Marie-Pierre Dube, Montreal
Wyeth Wasserman, UBC

Health-Economics: Craig Mitton, UBC
Adrian Levy, UBC

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- Eli Lilly
- Merck-Frosst
- Janssen Ortho
- Illumina Inc.

Students /Technicians

Hagit Katzov
Parvaz Madadi
Henk Visscher
Andrew Brown
Yannick Renaud
Catherine Carter
Terry Pape
Fudan Miao
Graeme Honeyman

ADR Surveillance Investigators and Surveillors

- *Vancouver*: Claudette Hildebrand, Dan Wright
- *Calgary*: Cheri Nijssen-Jordan, David Johnson, Lina Verbeek, Rick Kaczowka,
- *Edmonton*: Corrine Sikora
- *Winnipeg*: Kevin Hall and Shanna Chan
- *Toronto*: Gideon Koren, Shinya Ito, Miho Inoue
- *London*: Michael Rieder and Becky Malkin
- *Ottawa*: Elaine Wong and Regis Vaillancourt
- Hamilton: Amy Cranston
- *Montreal*: Jean-Francois Bussières, Denis Lebel and Pierre Barret
- *Halifax*: Margaret Murray, Darlene Boliver and Carol-anne Osborne