RGA

Genomics and Precision Medicine – The Impact on Insurance

ROSE 34th Annual Conference
September 20, 2018

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Agenda

- Define and discuss
  - Genomics
  - "Precision Medicine"
- Impact on Clinical Medicine
- Impact on Insurance – "What does it mean for us?"

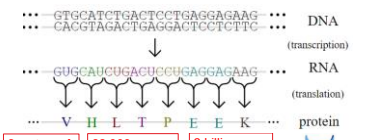
RGA 2

The World Today

Science Fiction → Science → Reality

RGA 3

Genetics Basics



40 trillion cells in the human body

23 chromosome pairs (one from each parent)

2 meters of DNA in each nucleus = "genome"

23,000 genes in 2% of the DNA = "exome"

3 billion ($3x10^9$) base pairs - TGCA

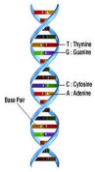
Genes make RNA that make proteins

Non-coding areas act as regulators

Single-nucleotide polymorphisms (SNP's) = Variation of a single base pair

Whole Genome Sequencing vs. Whole Exome Sequencing

Basis of DTC Testing and Polygenic Risk Scores



https://commons.wikimedia.org/wiki/File:Genetic_code.svg CC1.0

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What is Genomics?

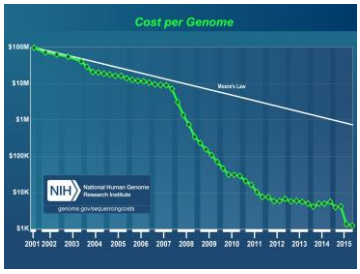
- **Genomics is the study of an individual's entire DNA sequence (genome) and how genes behave and interact**
- **Genomic medicine is the use of genomics to guide medical decision-making and patient care**
- **Genomics is an essential component of "personalized or precision medicine"**

Genomics vs. Genetics

- Genetics is the study of inherited traits and genes. (simplistic view)
- Genomics is the study of how a set of genes behave. (complex view)

RGA 5

Decreasing cost of genome sequencing



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Uses of Genomics

- Family planning (pre-conception)
- Prenatal screening
- Risk prediction (prior to disease)
- Disease diagnosis and prognosis
- Newborn screening
- Rare disease analysis
- Pre-clinical disease detection
- Disease recurrence detection
- Designing targeted therapies
  - Pharmacogenomics
  - Nutrigenomics
  - Cancer therapies
- Gene "editing"
  - CRISPR technology
- "Liquid" biopsies

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Genomics – Factors to Consider Regarding Test Results

Factors to Consider	
Analytical validity	Is the test accurate in detecting a particular genetic variant or its absence?
Clinical validity	What is the ability of a test to distinguish whether someone has, will, or will not develop a condition.
Clinical utility	What is the likelihood that the test will significantly improve patient outcomes? Is the result "actionable"?

Dandra C, et al. *South African Medical Journal* 2013;103(8):510-512.

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Genomics – Factors to Consider Regarding Test Results

- Monogenic disease = controlled by a single gene
- Polygenic disease (common complex) = controlled by many genes
- Genomic results can be predictive or diagnostic
  - Predictive = confers a probability of developing a condition
  - Diagnostic = confirms a clinical suspicion
- Multiple factors determine the manifestation of a gene
  - Environment, lifestyle, family history

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Genes are Not Fate

- Genetics and lifestyle factors are independent risk factors for coronary heart disease; High Genetic Risk : Low Genetic Risk **HR 1.91**
- In high genetic risk group, those with favorable lifestyle factors had a relative risk **46% lower** than those with unfavorable lifestyle factors

https://commons.wikimedia.org/wiki/File:Marathon_Runners.jpg CC 3.0

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Risk Prediction: Whole Genome Sequencing

- Whole genome sequencing
- Executive physical exam and specialized imaging
- Genomic and phenotype* analysis with machine learning to assess risk

(*Phenotype means the physical manifestation of a gene such as eye color or other traits.)

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Direct to Consumer (DTC) Genetic Testing

- Regulated by individual countries
- Can test for…
  - Disease risk and susceptibility
  - Traits or carrier status
  - Drug sensitivity
  - Ancestry and paternity

Approved 23andMe Testing	
Breast Cancer	Late-onset Alzheimer's
Parkinson's	Alpha-1 antitrypsin deficiency
Early-onset primary dystonia	Factor XI deficiency
Gaucher disease type 1	G6PD deficiency
Hemochromatosis	Hereditary thrombophilia
Celiac Disease	Age Related Macular Degeneration

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Genome Wide Association Studies (GWAS)

- GWAS outputs a "genotype"
- Identifies single nucleotide polymorphisms (SNPs) in the DNA and correlate with statistical probability for disease
- GWASs have been successful at identifying genetic variants associated with disease
  - 10 million SNPs discovered
  - 21000 SNPs associated with 600 diseases and traits
- Predictive ability is low

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Polygenic Risk Scores (PRS)

- Independent studies have developed PRS for:
  - Cardiovascular disease, diabetes, stroke, dementia, Alzheimer's disease, breast cancer, prostate cancer, colorectal cancer, schizophrenia (with mortality and suicidal behaviour), rheumatoid arthritis, obesity, depression, atherosclerosis, bipolar disorder, alcohol consumption, major depressive disorder, and many more!
- Many conclude that PRS can significantly improve the accuracy of disease risk prediction, even when added to the currently used set of predictors.

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Sample of PRS in literature

Condition	Genetic Variants	Difference in Risk
Coronary artery disease	60	2x (top to bottom 20%)
Coronary artery disease	49,310	1.8 to 4.5x (top to bottom 20%; depending on cohort tested in)
Type 2 diabetes	1000	3.5x (top to bottom 20%; after adjustment for standard risk factors)
Ischemic stroke	10	1.2x to 2x (top to bottom 20%)
Breast cancer	77	3x (top to bottom 20%)
Breast cancer (in women of East Asian ancestry)	44	2.9x (top to bottom 20%) – impressive given majority of SNPs associated with breast cancer risk have been conducted with European descendants
Prostate cancer	77	4x (top to bottom 20%)
Lung cancer	38	4.6x (top to bottom 25%)

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Genetic Testing offers *New and Independent* Predictive Powers

- This study tested the clinical utility of a PRS for coronary heart disease (CHD), in terms of lifetime CHD risk and relative to traditional clinical risk
- PRS tested in independent cohorts (combined n = 16,802 with 1,344 incident CHD events) and contrasted with the Framingham Risk Score (FRS)
- The HR for CHD from the PRS was 1.74 and 1.28 for the FRS. **Further, the PRS was largely unchanged by adjustment for known risk factors, including family history**
- Integration of the PRS with the FRS significantly improved 10 year risk prediction

RGA-KCL STUDY

Percentile	Standard cohort: Hazard ratio (95% CI)
0-1	0.66 (0.4 - 1.11)
1-5	0.41 (0.29 - 0.57)
5-10	0.77 (0.61 - 0.97)
10-20	0.78 (0.65 - 0.93)
20-40	0.81 (0.7 - 0.93)
40-60	1
60-80	1.15 (1.01 - 1.3)
80-90	1.54 (1.33 - 1.77)
90-95	1.43 (1.19 - 1.72)
95-99	1.92 (1.61 - 2.29)
99-100	2.78 (2.11 - 3.67)

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Does knowing your genomic profile influence behaviour?

- **Study to assess impact of communicating DNA based disease risk on risk-reducing health behaviors**
- **Looked at behaviors such as smoking cessation, diet, and physical activity**
- **Meta-analysis showed no impact on behavior when risk is known**

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Genomics and Cancer Detection

Forbes / Pharma & Healthcare

A Single Blood Test For All Cancers? Illumina, Bill Gates And Jeff Bezos Launch Startup To Make It Happen

Blood lust: Liquid biopsy startups Grail, Freenome raise record $1 billion in race to catch cancer early

Mar 1, 2017, 10:38am PST Updated Mar 1, 2017, 12:51pm PST

Amazon, Merck Invest $900M in Liquid Biopsy Startup

Thu, 03/02/2017 - 12:51pm 1 Comment by Ryan Bushey - Digital Editor - @R_Bushey

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The Promise of Liquid Biopsy

Pop Quiz!

- Q: True of False: While there are 38 companies all working furiously there are no *currently available FDA - approved* liquid biopsy tests?
- A: False! In June 2016, FDA gave approval to first liquid biopsy test (cobas EGFR Mutation Test) as a companion diagnostic test to erlotinib for treatment in non-small cell lung cancer
- 76% sensitive and 98% specific for EGFR mutations as compared to tissue

Research, Center for Drug Evaluation and. "Approved Drugs - Cobas EGFR Mutation Test v2." WebContent. Accessed January 17, 2017. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm504540.htm

RGA 19

The Promise of Liquid Biopsy

Why liquid biopsy? – Pop Quiz!

- Q: The turnaround time for Idylla (a PCR liquid biopsy test for BRAF mutations) is how long?

A. 4-6 weeks

B. 2 weeks

C. 1 week

D. 3 days

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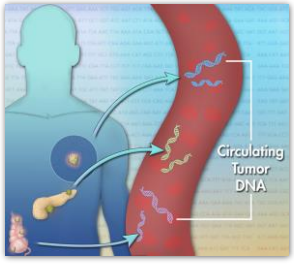
Liquid Biopsy

- **A primary solid tumour can shed whole cells or parts of DNA into the bloodstream and these are known as:**
  - **Circulating cell-free tumour DNA (ctDNA)**
  - **Circulating tumour cells CTCs**
- **A "liquid" biopsy is a blood test which can detect ctDNA or CTCs**



https://commons.wikimedia.org/wiki/File:Circulating-tumor-dna-article-_v300237192.jpg

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The Promise of Liquid Biopsy

Potential Advantages

- Turnaround Time
- Accessibility
- Easier to Repeat as Tumor adapts
- No Tissue Preservatives
- ? Mitigate Tumor heterogeneity
- Screening?

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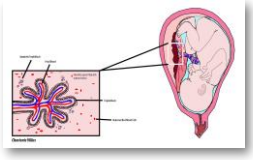
Genomics and Prenatal Screening

- **Measures fetal circulating free DNA in mother's blood**
- **Down syndrome**
  - **detection rate = 98.6%**
  - **False positive rate = 0.20%**
- **Trisomy 13 and 18 can also be detected**



https://commons.wikimedia.org/wiki/File:Cell_free_fetal_DNA_migrating_into_maternal_bloodstream.jpg Creative Commons License 3.0

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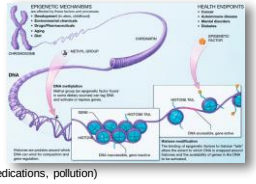
Epigenetics



- Epigenetics is the study of alterations to our genes which do **not** involve altering the *sequence* of the primary DNA itself
- Numerous factors have been implicated in the development of either beneficial or deleterious epigenetic changes. These include:
  - Diet and nutrition
  - Chemical exposures (e.g., tobacco, alcohol, medications, pollution)
  - Stress, depression, other psychological factors
  - Chronic diseases
  - Viral exposures
- Potential insurance use cases:
  - Predict all cause mortality: "epigenetic clock"
  - Tobacco, alcohol detection
  - Motivation within wellness programs
- Regulatory future is uncertain

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Precision Medicine

- **"Personalized" medical care based on an individual's genomics + lifestyle + environment**
- **Provides more accurate risk assessment and disease management**
- **Creates individualized therapies: "Give the right drug, at correct dose, aimed at specific targets"**

https://pixabay.com/en/target-arrow-bulls-eye-bullseye-2070972 Creative Common CC0

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U.S. Precision Medicine Initiative

- **$215 million USD**
- **Genetic profile of one million Americans**
- **Primary focus on cancer**

How will this impact long-term morbidity and mortality?

Source: https://www.nih.gov/precision-medicine-initiative-cohort-program

RGA 26

Pharmacogenomics

- **Individualized drug therapies based on an patient's genomic profile**
  - **Avoid drug side effects**
  - **Assist in the best selection of a drug at the right dose**
  - **More than 200 FDA-approved drugs have pharmocogenomic information in their labelling**

Now offered as an employee wellness benefit

May have increased upfront costs but overall savings

Source: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

RGA 27

Pharmacogenetic Product Applications

Dave's Pharmacogenetic "Profile"

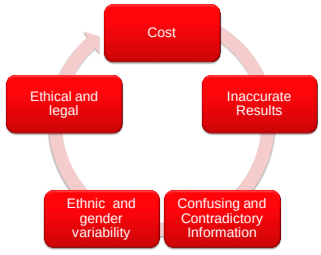
Lansoprazole	Gastroenterology	CYP2C19	CYP2C19 intermediate or poor metabolizers	Drug Interactions
Esomeprazole	Gastroenterology	CYP2C19	CYP2C19 poor metabolizers	Drug Interactions, Clinical Pharmacology
Omeprazole	Gastroenterology	CYP2C19	CYP2C19 poor metabolizers	Drug Interactions
Pantoprazole	Gastroenterology	CYP2C19	CYP2C19 poor metabolizers	Clinical Pharmacology
Pravastatin	Endocrinology	LDLR	LDL receptor mutation heterozygotes and homozygotes	Indications and Usage, Use in Specific Populations, Clinical Studies
Rosuvastatin (1)	Endocrinology	SLCO1B1	SLCO1B1 reduced function allele homozygotes	Clinical Pharmacology
Rosuvastatin (2)	Endocrinology	LDLR	LDL receptor mutation heterozygotes and homozygotes	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies

http://www.genomichealth.com/en-US/Colon/HealthcareProfessionals/RecurrenceScore/~/media/5A46E11D1DAD4025B0C361D1AFE61FC0.pdf

RGA 28

Barriers and Challenges – The Reality

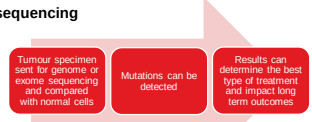
Are we back where we started?



RGA 29

Precision Cancer Treatment

- **Tumour sequencing**



Could be offered as a benefit for CI, cancer, and health policies.

- **Tumour sequencing may become the "standard of care" in oncology in the (near?) future**
- **The value of this testing remains controversial**

RGA 30

NCCN Guidelines for Tumor Sequencing

Cancer Type	Genes	Clincial Application
Acute Myeloid Leukemia	NPM1, FLT3, CEBPA, KIT	Risk Prognostication
Myelodysplastic Syndrome	JAK2, GATA2, TP53, ASXL1, ETV6, RUNX1, SF3B1, EZH2	Diagnosis and Risk Prognostication
Non Small Cell Lung Cancer	KRAS, EGFR, BRAF, ERBB2, RET, MET, ALKb, ROS1	Therapy Selection
Colorectal Cancer	KRAS, NRAS, MLH1, MSH2, MSH6, PMS2, BRAF	Therapy selection and cancer predisposition
Melanoma	KIT, BRAF, CDKN2A	Therapy selection and risk prognostication

Spencer, David H., and Timothy J. Ley. "Sequencing of Tumor DNA to Guide Cancer Risk Assessment and Therapy." JAMA 319, no. 14 (April 10, 2018): 1497–98

RGA 31

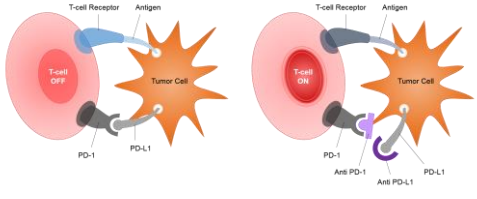
Immunotherapy

- **No longer only chemo, radiation, and surgery**
- **Adoptive T-cell therapies (CAR T)**
- **Checkpoint inhibitors**
- **Vaccines and oncolytic viruses**

Full access: http://www.rgare.com/knowledge-center/media/articles/cancer-immunotherapy

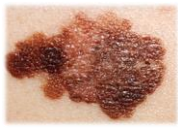
RGA 32

Immune checkpoint inhibitors

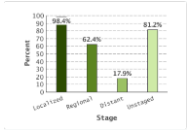


RGA 33

Late Stage Melanoma Treatment



- Prior to recent advances last drugs approved were dacarbazine in 1975 and interleukin-2 (IL-2) in 1988
- Response rate for dacarbazine is around 10% with an 18% overall 5 year survival for stage IV melanoma



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https://commons.wikimedia.org/wiki/File:DIG13605-028.jpg Public Domain

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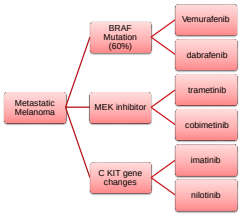
Late Stage Melanoma Treatment



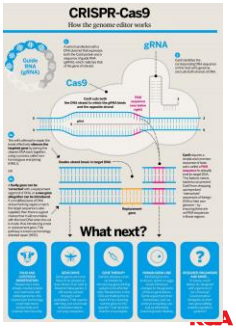
RGA 35

By Toni Barros from São Paulo, Brasil - Hello, Dolly!, CC BY-SA 2.0, https://commons.wikimedia.org/w/index.php?curid=5816342

RGA 36

What is CRISPR?

- **Clustered Regularly Inter-Spaced Palindromic Repeats**
- **Discovered in bacteria**
- **CRISPR allows genes to be edited with unprecedented precision, efficiency, and flexibility**



https://commons.wikimedia.org/wiki/File:CRISPR-Cas9-biologist.jpg Creative Commons 4.0

RGA 37

Current Clinical CRISPR Studies

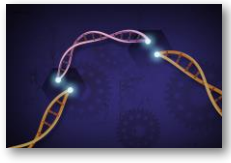
>20 at last count….

- Sickle Cell
- HPV
- Multiple cancers – Lung, prostate, breast, myeloma, melanoma, sarcoma
- Hemophilia
- Muscular dystrophy
- Hunter and Hurler Syndromes

RGA 38

What are the potential benefits of CRISPR?

- **Preventing or curing any disease with a genetic basis**
- **Eradicating HIV from T-cells**
- **Modifying mosquitoes so they cannot transmit disease**
- **Eliminating disease in embryos**
- **Creating "designer babies"?**
- **The possibilities are endless….**



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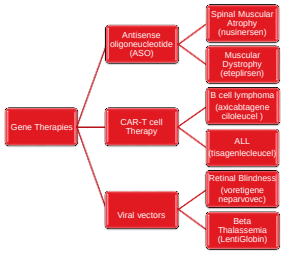
Gene Therapy: The Future is Now



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Genomics and Insurance

- Why is this issue important to discuss?
  - The technology is advancing rapidly
  - Genetic testing is becoming more common

RGA 41

Genomics: Key Questions in Life

- Anti-Selection vs. Mortality Lift
  - (What is Mortality lift?)
- Incorporation into Product
- Scope of Direct to Consumer testing
- Public Opinion
- Regulatory issues are complex

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Impact of genomics and precision medicine on the insurance industry...

- Underwriting (where allowed)
  - Enhanced risk stratification
  - High net worth, dynamic underwriting, attract healthier applicants, reduce lapses
- Post-issue
  - Wellness benefit – offer testing – motivate behavior?
  - Employee benefit
- Claims
  - Offer tumour genomic testing for cancer claim
- Health reimbursement
  - Pharmacogenomic testing could reduce costs
  - Cancer screening/tumour testing
  - Increased upfront cost but perhaps decreased long-term cost

RGA 43

New Challenge: Florida HB 855/SB 1106

- Defines genetic information
- In the absence of a diagnosis, no health, life, disability, or LTC insurer may cancel, limit, deny coverage, or establish differential premiums based on genetic information
- May not solicit genetic information, use genetic test results, or consider a person's decisions or actions relating to genetic testing in any manner for any insurance purpose

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RGA Genetics – Philosophy

Our global initiatives related to genetics are guided by a global committee in line with the 4 principles below:

- We believe that mandatory genetic testing should not be an underwriting or claim requirement
- We believe equality of information between insurance applicant and insurance company benefits both parties
- We will assess genetic tests disclosed at time of underwriting & claim, where legally allowed, using evidence-based principles
- We believe that access to genetic testing can improve patient care and could be incorporated into insurance products for policyholder benefit

In addition we:

- Conduct our own research to determine the impact of genetics on the insurance industry
- Follow closely developments in genetic research and the creation of laws pertaining to genetics

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RGA Genomic Initiatives

- Formed a Genetic Testing Work Group
- Representation to insurance industry associations and genetics sub-committees
  - CHLIA (Canada) and ACLI (USA)
  - Addressing challenges to limitations on the use of genetic information in underwriting
- Developed a white paper – to be updated third quarter 2018. Liquid Biopsy paper publication pending
- Product ideas incorporating genetic testing post-policy issue or at claim time

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Impact of WGS on Health Care costs

The MedSeq Project

Group	No Genetic Testing Mean Costs US$	Whole Genome Sequencing Mean Cost US$
Primary Care	2989	3670
Cardiology	9670	8109

"Short-Term Costs of Integrating Whole-Genome Sequencing into Primary Care and Cardiology Settings: A Pilot Randomized Trial | Genetics in Medicine." Accessed June 6, 2018. https://www.nature.com/articles/gim201835.

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Positive bends in the cost curve?

Representative Examples

- Hepatitis C
- Kawasaki
- PRS and Screening

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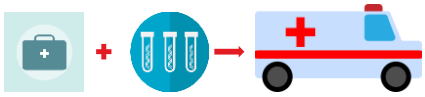
The UK Biobank is a uniquely powerful resource to study the importance of genetics in insurance

Our research questions

1. How accurately can the risk of mortality and major morbidity be estimated using multivariable prediction models based on detailed phenotypic information (medical history, physiology, behavioural and lifestyle risk factors)?
2. Can such prediction models be significantly improved - both in statistical and clinical / absolute terms - by including genetic data?



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Thank You!
Questions?
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