Medical Developments of Underwriting Interest

Mark Skillan, M.D.
Munich American Reassurance Company
Southeastern Actuaries Meeting
June 21, 2007
• Developments of Interest in Infectious Disease

• Genes, Mutations, Disease and Risk Assessment

• Genetic Testing Regulatory Update

• Stem Cell Update

• Second Cancers In Cancer Survivors
Infectious Diseases

- Tuberculosis
- Hepatitis
- Pandemic Flu
TB – Mycobacterium Tuberculosis

- TB most common cause of infection-related mortality in world
- > 2 Billion infected (1 in 3)
- 8-9 million develop active disease yearly
- 2 million die yearly (1 in 8)
TB Death Rate

- 7% industrialized west
- 20% Central and South America
- 35-40% parts of Asia and Africa
- >50% parts of Africa (HIV)
- Developing countries 95% cases, 98% deaths
TB Infection Cycle

- Exposure to symptomatic infected person
- Infection (silent) -> positive PPD skin test
  - usually not infectious
  - treatment goal - prevent disease
- Symptomatic Disease -> cough, weight loss, fever, etc. - infectious stage
  - treatment goal: cure disease
  - lack of treatment: illness, contagion, death
  - inadequate treatment: illness, resistant
    TB forms arise, contagion, death
MDR-TB

- Multi-drug resistant form – first cases 1990’s
- 2/3 cases in Russia, India, China
- 500,000 cases in 2005
- Resistant to first line drugs (INH, Rifampin)
- Requires second line drugs – at least 18 months
- Second line drugs – less effective, more costly, less available
XDR-TB

• Extensively Drug Resistant TB – 2005
• Resistant to INH, Rifampin plus also fluoroquinolones, and one or more of three injectable Rx’s
• 2-10% TB cases today
• Requires prolonged RX with 2\textsuperscript{nd} and 3\textsuperscript{rd} line drugs
• Outcome variable – cure currently possible
TB Remains a Treatable Disease

- Objectives of Therapy
  - Prevent or Cure Disease
  - Curb Further Spread
  - Prevent MDR and XDR-TB forms

- Requires
  - Early accurate Diagnosis
  - Prompt curative therapy
  - Patient compliance with meds
Obstacles to Cure/Eradication

- Access to care - delayed diagnosis
- Incorrect medication selection
- Inadequate duration of therapy
- Patient non-compliance
- Cost/Availability Issues
- HIV prevalence in some areas

Results of Failure: uninterrupted cycle of infection, more MDR and XDR cases
TB: Bottom Line

- Serious illness globally
- MDR and XDR problem likely to grow
- Controllable in industrialized countries
- New medical regimens and a vaccine are years away
- Be aware of TB risk in international business and in immigrants from high prevalence areas
Hepatitis A, B, C

- 1 in 3 in the US have been infected by HAV, HBV or HCV
- Impact for insurers (all lines) is significant and growing, especially for HCV
Hepatitis A (HAV)

- Spread by fecal oral route
- Mild to modest morbidity risk
- No chronic HAV infection known
- Limited/no mortality risk
- HAV vaccine 1995 plus better public awareness - 84% decline in US cases
Hepatitis B (HBV)

- Spread by blood products or intimate contact
- Modest morbidity and small mortality risk with acute infection
- 5-10% develop chronic HBV infection
  - 370 million worldwide have chronic HBV
- Significant long-term morbidity and mortality risk for 5-25% with chronic HBV
  - via cirrhosis, liver failure, liver cancer
  - duration of chronic infection is key factor
Chronic HBV in U.S.

- 60,000 new HBV infections in US annually
- 5-10% become chronic, but...
- 1 million in US with chronic HBV
HBV Control Initiative in US

- Blood supply screening for HBV
- Universal precautions
- HBV Vaccine (1984) prevents infection
  - for at higher risk groups (HCW’s, MSM, IVDU, etc)
  - universal childhood vaccination - new
- Effective antiviral therapies to treat chronic HBV now available and in use (interferon, ribavirin, etc); cure rate ~ 50%
  - Dramatic decline in new cases (less chronic HBV)
  - but…
HBV Control Challenge in U.S.

- Chronic HBV now most commonly found in immigrant populations from high prevalence areas
  - Many infected since birth or childhood
  - Many unaware of chronic HBV status
  - Long duration of infection by middle age - at increased morbidity/mortality risk
  - 1,000,000 cases chronic HBV in U.S. now
  - 500,000 Asian/Pacific Islanders alone
HBV Endemic Areas

- Southeast Asia
- Pacific Islands
- Indian Subcontinent
- Japan
- China
- Middle East
- Parts of Southern Europe and Africa
Bottom Line – Chronic HBV

- US remains low prevalence country for chronic HBV
- Vaccination plus effective therapies intended to reduce impact here
- HBV testing for cause (elevated LFT’s) among PI’s no longer commonly done – reasonable but...
- Chronic HBV among immigrants from high prevalence areas should not be overlooked in risk assessment
- Screening for HBV may remain a cost effective tool for persons born in high prevalence areas
Hepatitis C (HCV)

- Formerly known as non-A, non-B Hepatitis
- Infection mostly via blood products
  - 240,000 cases per year in 80’s
  - Blood supply screening added since then
  - 26,000 cases per year now
- 60-80% of those infected develop chronic HCV infection!
- 5 Million in US with chronic HCV disease
- Often silent
Impact of HCV

• Minimal to mild morbidity with acute infection, minimal acute mortality
• Significant long term morbidity mortality risk in 10-15% with chronic HCV -
  - late effects: cirrhosis, liver failure, liver cancer
  - Chronic HCV -#1 cause for live transplantation and hepatoma in US
HCV: Challenges Ahead

• Large number of infections in 1980’s and before
• Duration of chronic infection key to HCV morbidity/mortality
• An aging infected population now 20+ years out
• Disease complications costs expected to peak by 2015
• Direct medical costs may reach $10.6 B USD during 2010-2019
Stopping HCV Progression

- Rate of liver fibrosis development can be slow, moderate or rapid
- Limited ability to predict course at present:
  - following LFT’s – not reliable for HCV
  - serial liver biopsies: more definitive but unpopular (cost, risk, pain, error)
  - new FibroIndex (AST, platelet count, gammaglobulin level) – may lessen need for biopsy for some
  - determining viral genotype, following viral load are key

-> Treat those progressing and/or likely to respond to Rx
Predictors of Response to Therapy

**Primary**
- Low viral load at outset
- Genotype 2, 3, or 4 - 80% SVR after 24wks
  (genotype 1 - 45% SVR after 48wks)

**Secondary**
- Age at time of Rx
- Female
- Caucasian
- Normal BMI
- Absent co-morbidities
Bottom Line: HCV

- Chronic HCV an important disease in US
- Is often silent
- Effective screening is essential for insurers
- Major wave of HCV- associated morbidity/mortality is building – prepare accordingly
- Effective therapies exist and are key to morbidity and mortality reduction
- Therapeutic advances in short term (STAT-C, new protease inhibitors) should improve Rx success rates but will not likely be a silver bullet
Pandemic Flu
Business Continuity Planning 2007

RUN A SIMULATION OF OUR PRODUCTIVITY IF WE LOST HALF OUR WORKFORCE TO A PANDEMIC.

SHOULD I ASSUME WE LOSE THE PRODUCTIVE PEOPLE OR THE PEOPLE WHO ASK OTHER PEOPLE TO RUN PANDEMIC SIMULATIONS?

TRY BOTH WAYS.

OKAY. I'M DONE.

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Requirements for Pandemic

- A new influenza A virus must emerge
  - H5N1 is a new influenza A subtype

- It must infect humans causing serious illness
  - As of 6/12/07, 312 people infected with H5N1, 61% have died

- Efficient and sustained human to human transmission
  - Not yet documented
Occurrence of Influenza Pandemics and Epidemics

Introduction of hypothetical A HxNx virus

Significant minor variation in A HxNx may occur at any of these points. Epidemics may or may not be associated with such variations

Introduction of hypothetical A HyNy (major new subtype), variant A HxNx disappears

Infectious Disease Mortality in US 1900-2000

Source: Armstrong et al, JAMA, 1999; 281:61-66
Major Determinants of Mortality Rate in Pandemic

- Lethality of Circulating Viral Strain
- Ease of Transmission
- Size of Vulnerable Population
- Prevalence of Pre-morbid Conditions
- Rapidity of Spread
- Speed of Detection
- Accuracy of Diagnosis
- Adequacy of Prophylaxis and/or Treatment
- Accuracy of Death Certificates
Will Effective Human to Human Transmission of H5N1 Occur?

Three scenarios possible:

1. H5N1 remains in birds, other animals
   - fades in importance

2. Jumps directly from birds to humans
   - Postulated to have occurred in 1918

3. Combines with other influenza virus and then to humans
   - occurred in 1957 (Asian) and 1968 (Hong Kong)
   - Usually less virulent (partial immunity, etc.)
<table>
<thead>
<tr>
<th></th>
<th>Moderate (1957-like)</th>
<th>Severe (1918-like)</th>
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</thead>
<tbody>
<tr>
<td>90 million ill</td>
<td>90 million ill</td>
<td></td>
</tr>
<tr>
<td>(30%)</td>
<td>(1918-like)</td>
<td></td>
</tr>
<tr>
<td>45 million outPt care</td>
<td>45 million outPt care</td>
<td></td>
</tr>
<tr>
<td>865,000 hosp care</td>
<td>9,900,000 hosp care</td>
<td></td>
</tr>
<tr>
<td>128,750 ICU care</td>
<td>1,485,000 ICU care</td>
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</tr>
<tr>
<td>64,975 ventilator Pts</td>
<td>742,500 ventilator Pts</td>
<td></td>
</tr>
<tr>
<td>209,000 Deaths</td>
<td>1,903,000 Deaths</td>
<td></td>
</tr>
<tr>
<td>? $18 Billion health care cost</td>
<td>$180 Billion Health care cost</td>
<td></td>
</tr>
</tbody>
</table>
Health Care Capacity Issues

- 700 fewer hospitals from 1993-2003
  - 200,000 fewer acute care beds
  - 425 fewer ER’s
- Nursing shortages in many areas is routine
- 50% of ER’s already at or over capacity
- 33% of Hospitals already losing money
- On-time Delivery System for Critical Supplies
- Cost-cutting efficiencies limit “extra” equipment

* Net Effect → True Surge Capacity Non-Existent
### WHO stages of pandemic alert

<table>
<thead>
<tr>
<th>Interpandemic phase</th>
<th>Low risk of human cases</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>New virus in animals, no cases in humans</td>
<td>Higher risk of human cases</td>
<td>2</td>
</tr>
<tr>
<td>Pandemic alert</td>
<td>No or very limited human-to-human transmission</td>
<td>3</td>
</tr>
<tr>
<td>New virus causes human cases</td>
<td>Evidence of human-to-human transmission</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Evidence of significant human-to-human transmission</td>
<td>5</td>
</tr>
<tr>
<td>Pandemic</td>
<td>Efficient and sustained human-to-human transmission</td>
<td>6</td>
</tr>
</tbody>
</table>
# Pandemic Business Scenarios

<table>
<thead>
<tr>
<th>Stage</th>
<th>Business Continuity Issues</th>
<th>Human Infection</th>
<th>Economic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>• Public &amp; employee “awareness” – current situation</td>
<td>• No person-to-person transmission</td>
<td>• No measurable impact</td>
</tr>
<tr>
<td>3b</td>
<td>• Potentially distracting level of anxiety among public and employees</td>
<td>• No person-to-person transmission</td>
<td>• No measurable impact</td>
</tr>
</tbody>
</table>
| 4-5   | • Overseas travel restrictions imposed by government  
      • 24 hour media coverage, elevated concerns for personal/family safety  
      • Increase in employee absenteeism | • Person-to-person transmission has occurred overseas | • Overseas supply chains interrupted  
      • Some decline in equity markets |
| 6a    | • Regional travel restrictions within U.S. imposed by government  
      • Regional school & gov office closures  
      • Personal/family safety primary concern  
      • Sharp increase in employee absenteeism | • Excess mortality rate based on 1957 & 1968 pandemic “moderate” | • Significant but short-lived shock to equity markets  
      • Short-lived world recession |
| 6b    | • Widespread travel restrictions within U.S. and around the world  
      • School & gov office closures  
      • Work becomes a low priority to most  
      • Employee absenteeism is the norm | • Excess mortality rate based on 1918 pandemic “severe” | • Significant and lasting shock to equity markets  
      • World recession for extended period |
Pandemic Planning

• Pandemics- not considered preventable at this time – goal is to contain and reduce surge peak(s):
  - to effectively use resources available
• SOA: Insurers should lead planning efforts - partner with government, communities, hospitals, businesses and individuals in planning, risk management and recovery –
  - consider pro-activity an investment not an expense
Genetics, Mutations and Disease

Genetic Testing Regulatory Outlook

Status of Stem Cell Research
Genetic Testing

- **Hot topic in DC – S. 358 & HR. 493:**
  
  President willing to sign a bill

- **Potential problems for risk assessment**
  depending on:
  
  - definition of genetic test
  - lines to be covered
  - future legislative directions
Genetics

- Study of genes, the biologic unit of heredity, ->

  Learn structure and biochemical function ->

  Potentials ->
  - determine how body works normally and
  - what may contribute to or cause a disease
  - what may affect a disease’s course
  - what may determine an individual’s response to therapy
Medicine of the Past

Genetics & Medicine

Diagram with stages: Diagnosis, Therapy, Therapy Monitoring
Medicine in the 21st Century

Genetics & Medicine

- Predisposition Screening
- Targeted Monitoring
- Prevention or Early Recognition
- Diagnosis
- Therapy
- Therapy Monitoring
Landmarks in Genetics History

- 1859 Darwin - Origin of Species
- 1865 Mendel - notion/rules of inheritance
- 1867 Meisch - DNA (nuclein)
- 1882 Meisch - chromosomes
- 1908 Hardy-Weinberg - population genetics
- 1940’s Pauling - concept of molecular disease
- 1953 Watson & Crick - model structure DNA
- 1990 Human Genome project begins
- 2005 Complete sequencing of human genome finished
DNA the molecule of life

Trillions of cells
Each cell:
- 46 human chromosomes
- 2 meters of DNA
- 3 billion DNA subunits (the bases: A, T, C, G)
- Approximately 30,000 genes code for proteins that perform most life functions
Gene Function

Gene 1 → Protein 1
Gene 2 → Protein 2
Gene 3 → Protein 3
Mutations: Basis for Disease

- A change in DNA Code sequence in a gene along a chromosome
- Can be silent, beneficial, deleterious
- Effect depends on scale of change and area affected
  - Large scale versus small scale
  - Coding versus non coding region
Size Of Mutation

Large Scale Mutation
- Translocation

Small Scale Mutation
- Nucleotide Substitutions

ATCGAATC

ATGGAATC
Causes of Mutations

- Errors in DNA replication process (accident or chance)
- Mutagen effect
  - UV, X-rays, Radiation
  - chemicals that bind/react with DNA
  - chemicals whose metabolites generate reactive oxygen that damages DNA
How Mutations Arise
Beneficial Mutation

CCR5 Facilitates HIV Entry into the Cell

Mutated or Nonfunctional CCR5 Protects Against HIV Entry into the Cell
Mutation Repair

- Is the norm
- Complex biochemical repair mechanism exists
- Routinely “proof reads” the code, repairs as needed
- Failure to repair -> cellular dysfunction medical illness, tumor, etc
Gene Studies

• Detects mutations
• Links mutations to disease manifestations
• Provides potential point(s) of intervention for targeted therapies:
  - gene repair (future)
  - supplement deficient gene product
  - counteract excessive gene product
Disease Cause Continuum

ENVIRONMENT

GENES

HEMOPHILIA
CYSTIC FIBROSIS
FAMILIAL COLON OR BREAST CANCER
ALZHEIMER'S DISEASE
STROKE
DIABETES
CARDIOVASCULAR DISEASE
LUNG CANCER
MOTOR VEHICLE ACCIDENT
ASTHMA
Single Gene Disorders

- Follows Mendelian laws of inheritance
  - predictable disease incidence
- Little environmental contribution
- Well studied diseases, genetic tests available,
  few in number:
  - Hemophilia
  - Sickle Cell Disease
  - Huntington’s Disease
  - Cystic Fibrosis
Common Complex Diseases

• No clear Mendelian pattern of inheritance (not directly predictable)
• Genetic and environmental contributions likely
• Variable penetrance/expression
• Occurrence of protective and susceptibility genes
• Familial aggregations may be seen
• Includes most of the common diseases we underwrite:
  CVD, CA, Schizophrenia, DM, HCVD, AD, CVA, obesity,....
Familial Aggregation

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Risk %</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Degree Relative</td>
<td>3 to 5</td>
</tr>
<tr>
<td>Second Degree Relative</td>
<td>2 to 3</td>
</tr>
<tr>
<td>Third Degree Relative</td>
<td>1</td>
</tr>
<tr>
<td>General Population (Northern Europe)</td>
<td>0.1</td>
</tr>
</tbody>
</table>
CVD - A Common Complex Disease

Diagram showing the interaction of various genes and factors related to cardiovascular disease.
Recent Testing Advances

- Breast Cancer: MammaPrint – measures 70 gene markers in tumor – score predicts likelihood for recurrence in 10 years in Stage I or II node negative breast Ca
- Leukemia: newly discovered 13 gene MicroRNA expression profile (signature) in CLL indicates prognosis (time from diagnosis to need for treatment); may clue pathogenesis as well
Genetic Testing Regulatory Challenge: Perception vs. Reality

- Except in rare single gene disorders, a genetic mutation often does not equal disease.
- Most common disorders are multi-factorial and often can be favorably influenced by early diagnosis, treatment and/or behavioral changes (CAD, DM, BRCA-1/2).
- All of us likely have one or more such mutations.
- Genetic testing not cost effective for insurers for single gene or common complex disorders.
Challenge: Should Private Insurers Have Access to Medical History?

- Genetic discrimination not documented to be a problem in private insurance market
- ADA (1990) and HIPPA (1996) address primary concerns expressed plus
- State laws already address employment issues (37 statutes) and health insurance issues (47 statutes)
- New legislation risks - a broadened definition of a genetic test, loss of access to full medical records, ? loss of family history, ? further micromanagement of risk assessment to follow
Stem Cells

• Usual source is unused fertility clinic embryos
• Pleuri-potent or omni-potent embryonic cells
• Further development of these cells depends on environment – hormonal, biochemical, etc.
• Theoretical potential to generate cells to use to repair or replace damaged or defective cells
• Current efforts stymied by ban on federal funding of research on human embryos (Dickey-Wicker Amendment, 1996)
Stem Cells

- Existing 20 stem cell lines old, problematic
- Federal funding greatly missed
- Privately funded and State funded research ongoing
- Alternative ways to artificially produce stem cells also being studied
From Skin Cells to Stem Cells

Researchers have developed a technique for creating stem cells without the controversial use of eggs or embryos.

**NEW TECHNIQUE**

- Adult skin cells
  - Gene-carrying viruses
  - Mixture of cells
  - Stem cells

The process begins with a large number of adult skin cells. The skin cells are exposed to viruses, each carrying one of four critical genes. Cells that absorb all four genes are somehow converted to stem cells. Researchers kill any unconverted cells, leaving behind viable stem cells.

**EXISTING TECHNIQUE**

- Adult skin cell
  - Unfertilized egg
  - Developing embryo
  - Blastocyst
    - Inner cell mass
  - Embryonic stem cells

In therapeutic cloning, the nucleus of an adult skin cell is inserted into an unfertilized egg with its nucleus removed. The egg reprograms the adult nucleus back to its embryonic state and the egg begins to divide. After several days a blastocyst forms. Stem cells can be taken from the blastocyst’s inner cell mass, which destroys the embryo.

*The New York Times*
Second Tumors in Cancer Survivors

- In Same Organ or Different Organ/System

Causes

- Genetic susceptibility – complex interplay
- Therapy-related – response to chemo and/or radiation exposure
- Environment
- Behavioral factors – tobacco, alcohol, BMI, stress, activity...
Childhood Cancer Survivors

- Survivors of certain cancers have lifetime RR of 10-20 for second malignant neoplasm, e.g.,
  - MOPP- associated leukemia (ANLL)
  - radiation treatment-associated cancer of breast (RR 14), thyroid, CNS, skin, sarcoma

-> Other than recurrence of the primary tumor, a second malignancy is commonest cause of death among long term childhood cancer survivors
# Second Malignancies in Adults after Hodgkin’s Disease Treatment

<table>
<thead>
<tr>
<th>2nd Site</th>
<th>Observed</th>
<th>Expected</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>747</td>
<td>195</td>
<td>3.8</td>
</tr>
<tr>
<td>Leukemia</td>
<td>116</td>
<td>5.2</td>
<td>22-95</td>
</tr>
<tr>
<td>NHL</td>
<td>112</td>
<td>6.0</td>
<td>18.5</td>
</tr>
<tr>
<td>Solid Tumors</td>
<td>519</td>
<td>184</td>
<td>2.8-4.3</td>
</tr>
</tbody>
</table>
Second Malignancies After Treatment for:

- NHL – RR 1.2 to 1.8 by 10 yrs
- Ovarian – RR 1.3 by 20 years
- Testicular – RR 1.43

Risk varies: for some cancers the risk for 2\textsuperscript{nd} cancer peaks a few years after initial tumor treatment then declines, others - risk peaks at \(~10\) years out then declines, still others - risk increases or remains stable over lifetime
Bottom Line- Second Malignancies

- Cancer treatment continues to improve...
- Growing population of survivors of childhood and adult cancers -> Growing population of persons at increased risk for a second cancer
- Outcome with second cancer often less favorable - high morbidity/mortality
- Limited data at this point for > 10-15 years
- More recent/current regimens may be less toxic
• TB a global issue; MDR and XDR worrisome developments
• HBV significant world risk and in the US in immigrant from endemic lands
• HCV-related morbidity and mortality on the rise
• For HBV and HCV diagnosis and treatment are key to reducing morbidity and mortality risks
• Genetic testing regulation potentially pivotal for medical risk assessment in the US
• Stem cell potential remains unrealized
• Be aware of growing population of cancer survivors who may be at increased risk for a second cancer and early mortality
Thank you
Key Resources

www.pandemicflu.gov

www.cdc.gov

www.acli.com
In the event of pandemic influenza, businesses will play a key role in protecting employees’ health and safety as well as limiting the negative impact to the economy and society. Planning for pandemic influenza is critical. To assist you in your efforts, the Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) have developed the following checklist for large businesses. It identifies important, specific activities large businesses can do now to prepare, many of which will also help you in other emergencies. Further information can be found at [www.pandemicflu.gov](http://www.pandemicflu.gov) and [www.cdc.gov/business](http://www.cdc.gov/business).

### 1.1 Plan for the impact of a pandemic on your business:

<table>
<thead>
<tr>
<th>Completed</th>
<th>In Progress</th>
<th>Not Started</th>
</tr>
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</tbody>
</table>

Identify a pandemic coordinator and/or team with defined roles and responsibilities for preparedness and response planning. The planning process should include input from labor representatives.

Identify essential employees and other critical inputs (e.g. raw materials, suppliers, sub-contractor services/products, and logistics) required to maintain business operations by location and function during a pandemic.

Train and prepare ancillary workforce (e.g. contractors, employees in other job titles/descriptions, retirees).

Develop and plan for scenarios likely to result in an increase or decrease in demand for your products.
Additional Pandemic Resources

- International / World Health Organization: www.who.int/en
- Europe: www.eurosurveillance.org/index-02.asp
- European Centre for Disease Prevention and Control: www.ecdc.eu.int
- American Medical Association: www.ama-assn.org
- Insurance Information Institute: www.iii.org
- Moody’s Special Comment Bird Flu Risk for U.S. Life Insurers: a Tail event April 2007
- National Association of Securities Dealers: Notice to Members 06-31