Digital Pathology
The last missing link in personalized medicine

Ajit Singh, Ph.D.
Chief Executive Officer
BioImagene
A car for every Indian
Citizens cannot be denied the comfort they deserve; innovators their recognition

A couple of days back, Tata launched the much-hyped Rs 1-lakh car, Nano. The car is believed to be the cheapest in the world and is expected to revolutionise travelling in India. The car looks good and also seems to come with a decent set of features. Considering that hardly any Indian company can afford to research and innovate, Nano is a significant achievement for the Tata. The Indica was launched in a market that wasn’t very competitive, however that isn’t true about the car market today. The Tata’s belief in the Nano’s ability to take on global competition and the years of effort that has gone into creating the car, sure make the venture one of the most admirable in recent times. This is amply reflected through the 100s of positive comments about the car, Ratan Tata and Tata Motors that are all over the Internet.

The Nano is also good for the spirit of India. Businesses and entrepreneurs can find motivation in the fact that innovators get loads of appreciation from Indian society. For the general public, just knowing that India can design and produce its own car is a good morale boost. I am sure there would be many youngsters wanting to work for Tata Motors one day, primarily because of the innovation displayed by the company in recent years. Having said that, the Tata small car has also come in for a lot of criticism not just from those opposed to the car manufacturing plant in West Bengal but also from many environmentalists. The criticism from environmentalists spawns from the fact that it is pretty much a certainty that cars like the Nano will kill Indian cities.

Looking at the capabilities of our administration, we can be quite sure that the infrastructure will not match the rapid growth in vehicles. Even if the infrastructure did scale up fast enough, more roads and more cars are essentially eco-unfriendly. In the climate change story, cars are the villains. India has lately adopted a number of American customs and it now looks all set to adopt the concept that has made America the biggest polluter in the world, that of one person one car. So the Nano sure is a great achievement, but is it good for India?

There are suggestions that the Nano should be heavily taxed so that it doesn’t stay cheap and become abundant. This seems improper because if Tata has succeeded in keeping their costs down, it’s not right to penalise them for their efficiency. Also it is not like alcohol or cigarettes where the society as a whole questions the judgement of the individual and so feels the need to regulate and discourage consumption. When politicians don’t want people to think rationally they normally throw in an emotional argument that ensures that the brain is switched off and the heart decides. I will try something similar. A good friend of yours with a wife and two kids is driving down an overcrowded city road on his scooter. All four are breathing loads of pollution. The lady is somehow balancing the child, the father is sweating in his attempt to manoeuvre his family safely home. The worst case scenario will be if they crash. But even if they don’t, the kids are being exposed to pollution that will have a serious long term impact on their health. The parents undergo tremendous stress in their attempt to ensure the well being of the family.

Would making a car available to 1000s of such families be a good thing or bad? Good for the individual but bad for the nation is what some might say. But what if the cheap car saves a 1000 innocent lives every year, of people who would have otherwise perished in the accident if they were riding a two-wheeler? Is that a good enough return on investment for India? If families are not exposed to direct pollution as happens on a two-wheeler, would India benefit from the savings in healthcare? And the comfort and security inherent to owning a car. So the option is to provide an even better alternative to the private car, one that’s people, city and environment friendly. Only a good public transport system seems to fit these requirements. India should aim for a situation where a person has to choose between public transport and a car and not a two-wheeler. Public transport should be so obviously superior and convenient that the citizen uses his car only for luxuries like taking the family out for a picnic and never for his daily commute. For example, even with Mumbai’s mediocre public transport system, there are 1000s of car owners who prefer to use trains for their daily travel.

Can private enterprise play a role in improving the public transport mechanisms in India? Why not? The prospect of Tata Bus Transport (TBT) and a Reliance Bus Transport (RBT) competing to sell me a bus ticket for a Deccan Gymkhana to Lohegaon airport ride, sounds sounds cool. Doesn’t seem very likely, but can’t deny that the prospect is exciting.

(Guest Columnist can be reached...
what is this?
a low-end car?
Building the world's cheapest car

The cheapest car in the world, set to sell for just $2,500, is being unveiled at the Delhi Auto Expo by the Indian car manufacturer Tata Motors. The "one lakh"—slang for 100,000 rupees—people's car is aimed at the country's 65 million scooter riders currently unable to afford a car.

- **Rear-mounted engine:**
  - Two-cylinder petrol, 660cc, 133bhp, built by Bosch
  - **Fuel efficiency:** 60mpg
  - **Top speed:** 75mph
  - **0-60mph:** 21 secs

- **Instruments:**
  - Limited to analogue speedometer, odometer and fuel gauge

- **Front luggage compartment:**
  - Holds battery, windshield washer bottle. Room for single suitcase

- **Weight saving:**
  - Extensive use of plastic

- **Cost saving:**
  - No radio, power steering, air conditioning, emissions control, antilock brakes, air bags, safety beams

- **Rear wheel drive:**
  - Uses continuous variable transmission, lighter alternative to manual or automatic

- **Wheel bearings:**
  - Strong enough to drive car at 45mph, but will quickly wear out at higher speeds
a high-end motorcycle?
what is this?
a low-end ultrasound?
a high-end stethoscope?
what is this?
another disruptive innovation
SUPPORT CHRIS AVENIR

Organizations - Advocacy Organizations
For all those who have read the Metro or the Eyeopener, then you should all know who Chris Avenir is by now. If not, you fail. In a nut shell, he is facing expulsion from Ryerson for becoming an admin for a group, much like this one. Read the following article from the Metro for a much more detailed summary and charges.

http://www.metronews.ca/story_local.aspx?id=109718&searchtype=1&fragment=False

The star is also cool.
http://www.thestar.com/article/309855

So are we not allowed to talk to other people about school work? Are we not allowed to teach others and impart our wisdom? Are we not allow to share ideas?

If you feel that this is an outrage and that Chris's charges should be dropped, please simply join this group and share these articles with all your friends just to show your support for this good man!

His hearing is taking place on Tuesday March 11th at ENG 3rd floor, Room 358 from 3:00-4:30, drop in or after to show support. Bad thing is, only those allowed in.

Group Type
This is an open group. Anyone can join and invite others to join.

Admins
- Leo Chan (Ryerson) (creator)
The Presidential Inauguration
Barack Obama swears in as the 44th president of the United States
all great examples of disruptive innovation
but, in order to see that, we must look unconventionally
In the **conventional** world of “looking”,
it is easy to see what is going on,
reality is recognizable,
even though sometimes fuzzy, the picture is understandable.
Then things start to look funny ...
they become harder to recognize
... and disjointed,
... but you can still tell what is going on.
However, it gets harder…
... and harder
and finally it becomes impossible
to see what is going on...
... by looking at things the *conventional* way.
our onus is to figure out the pattern that lies hidden underneath the apparent chaos on the surface
to see through Picasso’s outer shell and uncover...
the Velazquez that lies behind it.
our onus is to figure out the pattern
space :: pattern

time :: trend
trends
two trends triggered by disruptive innovation
2 things
you simply could not do at all before

1 things
you can do at a significantly lower cost
what did digital-ization transform in radiology?
ca 1900
X-Ray

ca 2000
CT

31,567 asymptomatic persons at risk for lung cancer using low-dose CT identified 484 with stage I lung cancer.

Surgery improved five-year survival.
15 years of digital radiology

New:
- 3D Visualization
- Quantitative analysis (Cardiology, Oncology)
- Fusion – anatomy and physiology
- Contextual access to anatomy atlas at POC
- Contextual access to “similar cases” at POC
- Contextual access to expert opinion at POC

Productivity up by 20%
Report turn-around time down from 3 days to 3 hours
Radiology study availability up from 60% to nearly 100%
“Handling errors” down – undocumented

Clinician viewing up by a factor of 2
Comparison with prior studies up by a factor of 5
Screening (breast, lung, colon) up by a factor of 10
1. things
   you can do at a significantly lower cost

2. things
   you simply could not do at all before
1. automate
   standard of care

2. redefine
   standard of care
what did digital-ization transform in radiology?
what can digital-ization transform in pathology?
quantitative comparison  
improve report turnaround time  
case sharing and collaboration  
pathology 2.0  
education  
archiving and retrieval  
tumor boards  
remote case review  
remote slide “availability”  
efficient primary diagnosis  
consultation and second opinions  
research and clinical trials  
reporting  
data mining for decision support  
CME and proficiency testing  
reduce handling errors  
QA  
quantification  
image analysis  
remote frozen sections  
improve slide “availability”  
personalized medicine  
companion algorithms  
reporting
Transformation Potential…

1. Improve report turn-around time
   Archiving and retrieval
   Tumor boards
   Remote case review
   Efficient primary diagnosis
   Reduce handling errors
   Improve slide availability
   Quantification

2. Quantitative comparison
   Case sharing and collaboration
   Image analysis
   Remote frozen sections
   Data mining for decision support
   Personalized Medicine
2 things
you simply could not do at all before

1 things
you can do at a significantly lower cost
1. automate
   standard of care

2. redefine
   standard of care
Radiology – Pathology Juxtaposition

Analogous

Convergent

Complementary
companion algorithms™

software applications

scanners
companion algorithms™

software applications

scanners
companion algorithms™

software applications

scanners
companion algorithms™
Image Analysis for H&E

- Epithelial recognition
- Nuclear morphometric analysis: size, shape, chromatin pattern
- Mitosis detection
- Gland detection
Epithelial recognition

Original TMA image

Epithelial cells: red
Stromal cells: yellow
Nuclear morphometry

Nuclei of carcinoma cells are larger than both stromal and normal cells:
- 5 - 10 μ (yellow)
- 11 - 15 μ (green)
- 15 – 25 μ (red)
Mitosis detection

Original image

Identified mitoses
Gland detection
Putting it together

SBR Scoring: Breast Cancer

Gleason Scoring: Prostate Cancer
Breast Panel – Image Analysis for IHC
Her2-neu IHC: Membrane Algorithm
ER/PR IHC: Nuclear Algorithm

<table>
<thead>
<tr>
<th>Results</th>
<th>Nuclear</th>
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<tbody>
<tr>
<td>Non Stained Cell Count</td>
<td>95</td>
</tr>
<tr>
<td>Stained Cell Count</td>
<td>314</td>
</tr>
<tr>
<td>Percent Positivity</td>
<td>77</td>
</tr>
</tbody>
</table>
Cytoplasmic Algorithm
Digital Scoring of Her2-neu FISH
Digital Scoring of Her2-neu CISH

- Dark red: large cluster (+)
- Light red: small cluster (+)
- Blue: polysomy (-)
- Green: Nucleus diploid (-)

Final: 154 nuclei—51 single, 21 polysomy, 41 small+, 41 large+
Prostate Panel: IHC triple stain algorithm

P504s (red, cytoplasmic stain)

K903 (brown, cytoplasmic stain)

p63 (brown, nuclear stain)
Red glands (Red only): Adenocarcinoma
Green glands (Brown only): Benign
Yellow glands (Red + Brown): HGPIN
Ki67 Scoring in CNS Glial Tumors

56%
Companion Algorithms: Breast Cancer

Her2-neu IHC, FISH, and CISH: selection of patients for Herceptin®

ER/PR scoring selection of patients for anti-estrogen therapy
Companion Algorithms: Colon and Lung

Colon Cancer

- EGFR testing (IHC/FISH) for selection of patients for Erbitux®
- Thymidylate synthase testing for selection of patients for anti-folate based chemotherapy
- MLH/MSH testing for identification of patients with hereditary nonpolyposis colorectal cancer (HNPCC)

Lung cancer

- EGFR testing (IHC/FISH) for selection of patients for Tarceva® and Iressa®
- ERCC1 and RRM1 testing (IHC) for selection of patients suitable for chemotherapy drugs - prediction of response to cisplatin and gemcitabine
Companion Algorithms: Other Cancers

Prostate Cancer
- Therapy selection - AR IHC for selection of patients for anti-androgen therapy
- Prognostic FISH markers - 21q22 Rearrangements (TMPRSS2)

Gastrointestinal Stromal Tumors
- CD117 testing for diagnosis and selection of patients for Gleevec® therapy

Oligodendrogliomas
- FISH testing for deletions at chromosomes 1p and/or 19q for predicting response to chemotherapy

Lymphomas/leukemias – variety of tests (including IHC and FISH) crucial for diagnosis, prognosis, and treatment decisions
companion algorithms™

enable companion diagnostics
companion algorithms™ enable personalized medicine
Enable Personalized Medicine
“What diagnosis/care would be optimal for this patient”

Key Enabler
“Emergent Knowledge”

Support evidence-based medicine
“How should patient be treated per guidelines”
1. Collection of large databases of patient data and external medical knowledge

2. Creation of personalized knowledge models

3. Application of personalized knowledge models in clinical workflow
Personalized Medicine: How specifically?

Probabilistic Inference Over Time

Clinical Decision Support Application

Combine Conflicting Local Evidence

Probabilistic Inference Over Time

Extraction

Extraction

Pathology Images

Radiology Images

Lab Pharmacy Text Notes

Proteomics

Genomics

Personalized Knowledge Models
digital pathology...

... is that “last missing piece”
Identification of biomarkers whose expression correlates with:

1. Behavior of disease (for prognosis)

2. Response of disease to specific therapeutic agents
... the role of quantification will increase
companion algorithms™
will redefine standards of care
PathXchange

Case of the Week

Tumor in the right colon

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Browse interesting cases from around the world

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Share your cases and slides with colleagues

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Search our expanding global knowledge base

Learn
Learn about the latest advances

Ask
Ask experts for their opinion on your case
● **Browse** interesting cases from around the world
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● **Search** our expanding global knowledge base
● **Learn** about the latest advances in the field
● **Ask** experts for their opinion on your case
Browse cases in a category

Soft Tissue (20)

Most Recent  Most Discussed  Most Viewed  Highest Rated

85-y/o female with subcutaneous leg mass 06/02/2009
pinkoos  Christus St. Catherine Hospital
Tags: Soft Tissue
The surgeon "shelled out" a 4.5 cm lobulated subcutaneous mass that he thought was a lipoma.

Soft Tissue 1  06/27/2009
Mahul B. Amin, MD  Cedars Sinai Medical Center
Tags: Soft Tissue

Soft Tissue 2  06/27/2009
Mahul B. Amin, MD  Cedars Sinai Medical Center
Tags: Soft Tissue

Soft Tissue 3  06/27/2009
Mahul B. Amin, MD  Cedars Sinai Medical Center
Tags: Soft Tissue
Tumor in the right colon

Allen M. Gown, M.D.
Tags: Gastrointestinal

63 year old female with tumor in the right colon.

<table>
<thead>
<tr>
<th>Case Overview</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Age:</td>
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<tr>
<td>Sex:</td>
<td>female</td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
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<tr>
<td>H &amp; E</td>
<td>Negative</td>
</tr>
<tr>
<td>ER</td>
<td>Negative</td>
</tr>
<tr>
<td>CK20</td>
<td>Negative</td>
</tr>
<tr>
<td>CK7</td>
<td>Negative</td>
</tr>
<tr>
<td>GCDFP-15</td>
<td>Negative</td>
</tr>
<tr>
<td>ITF</td>
<td>Loss of expression</td>
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<tr>
<td>MLH-1</td>
<td>Loss of expression</td>
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<tr>
<td>MSH-2</td>
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<td>MSH-6</td>
<td>No loss of expression</td>
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<tr>
<td>No Primary</td>
<td>Negative</td>
</tr>
<tr>
<td>OSCAR</td>
<td>Negative</td>
</tr>
<tr>
<td>p03</td>
<td>Negative</td>
</tr>
<tr>
<td>PAX-2</td>
<td>Negative</td>
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<tr>
<td>PMS2</td>
<td>Loss of expression</td>
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<tr>
<td>Synaptophysin</td>
<td>Negative (artifact)</td>
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<tr>
<td>TTF-1</td>
<td>Negative</td>
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<tr>
<td>Villin</td>
<td>Focally positive</td>
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<tr>
<td>WT-1</td>
<td>Negative</td>
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Browse similar cases

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<th>Negative</th>
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<td>Negative</td>
</tr>
</tbody>
</table>

Similar Cases

- **Crohn's Disease**
  - Stephen W. Chensue
  - Tags: Gastrointestinal

- **Gi 10**
  - Mahul B. Amin, MD
  - Tags: Gastrointestinal

- **Gi 9**
  - Mahul B. Amin, MD
  - Tags: Gastrointestinal

Good case

Bob Smith, M.D.
Stanford University School of Medicine

Thank you for sharing this case. I have a similar case and have the same diagnosis.
Create a case

Create Case

Title: *
Liver mass

Pathology Categories *
- Blood & Bone Marrow
- Cytology
- Genitourinary
- Kidney
- Other
- Thoracic
- Bone
- Dermatopathology
- Gynecological
- Liver & Pancreas
- Pediatric Neoplasms
- Breast
- Endocrine
- Head & Neck
- Lymphoma
- Prostate
- Cardiovascular
- Gastrointestinal
- Immunohistochemistry
- Neuropathology
- Soft Tissue

Tags:
clear cell myomelanocytic tumor
A comma-separated list of terms describing this case.

Description:
Liver mass in a 47 year old female
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   919 Hermosa Ct
   Sunnyvale, CA 94085
   U.S.A.

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Special Instructions:
Search for cases, users...

Search

Enter your keywords:

prostate

Search

Search results

Prostate Case #31
... 05/30/2009 Prostate Case #31 Biologicene Rob Monroe. ... Tags: Prostate Input from more ... 
Case - Rob Monroe, M.D., Ph.D. - 06/02/2009 - 06:40 - 1 comment - 0 attachments - 0 groups

Prostate case
... 05/22/2009 Prostate case Bi-Biomics (UltraLight Histology) ... Tags: Prostate Artifact free detail makes diagnosis easier ... 
Case - Tom Dornedinger - 05/28/2009 - 09:41 - 0 comments - 0 attachments - 0 groups

Prostate Case #30
... 05/30/2009 Prostate Case #30 Biologicene Rob Monroe. ... Tags: Prostate (Prostate) ... 
Case - Rob Monroe, M.D., Ph.D. - 06/02/2009 - 06:42 - 0 comments - 0 attachments - 0 groups

Prostate Case #1
... 05/29/2009 Prostate Case #1 Biologicene Rob Monroe, ... Tags: Prostate 65 year old male with elevated PSA ... 
Case - Rob Monroe, M.D., Ph.D. - 05/30/2009 - 21:53 - 0 comments - 0 attachments - 0 groups

Prostate Case #28
... 05/30/2009 Prostate Case #28 Biologicene Rob Monroe. ... Tags: Prostate (Prostate) ... 
Case - Rob Monroe, M.D., Ph.D. - 06/02/2009 - 13:01 - 0 comments - 0 attachments - 0 groups
Search only pathology sites

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Enter your keywords:

prostate

Search results

PathSearch is the first vertical search exclusively for the Pathology domain. Search results only come from top Pathology-related websites so they are more relevant. If you found that a website is excluded by mistake, please drop us an email so we can include it.

Results 1 - 10 for prostate. (0.23 seconds)

Refine results for prostate:
Tests & Diagnosis Symptoms Treatment Causes/Risk Factors References

Prostate Cancer Center Treatments Symptoms Detection Stages ...
Prostate cancer is diagnosed in an estimated 80% of men who reach age 80. Find in-depth prostate cancer information here on prevention.
www.webmd.com/prostate-cancer/default.htm

Prostate gland and seminal vesicles
Within true pelvis between bladder neck (base of prostate) and urogenital diaphragm / levator ani muscle (apex of prostate) ...
www.pathologyoutlines.com/prostate.html

Masturbation and Prostate Cancer Risk
Jan 27, 2009 ... Frequent masturbation is a sign of higher prostate cancer risk in younger men, but a sign of lower risk in older men, a UK study shows.
### My relationships

<table>
<thead>
<tr>
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<tr>
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<td>Keith J. Kaplan, M.D.</td>
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<tr>
<td>Baystate</td>
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</tbody>
</table>
Read pathology blog feeds

Feed aggregator

Tabulating the Cost of Undiagnosed Diabetes in the U.S.
Lab Soft News - Mon, 06/01/2009 - 04:09

I have posted a number of previous notes about the cost of care for various chronic disease (see: Seeking Solutions to the Chronic Disease Epidemic, Cost Savings Associated with Home-Based Physiologic Monitoring) with a special focus on diabetes (see: The... Bruce Friedman

Categories: Pathology Blogs, Pathology News

Exciting new application from Bruker Daltonics
The Daily Sign-Out - Sat, 05/30/2009 - 08:22

Digital Pathology Blog has an interesting post on a new application for research which fuses digital slide imaging with MALDI mass spectrometry. This is huge! One of the weaknesses I see with proteomics is that in using mass spec analysis... Mark D. Pool, M.D.

Categories: Pathology Blogs

The impact of digital imaging in the field of cytopathology
Digital Pathology Blog - Fri, 05/29/2009 - 16:31

Interesting paper by Dr. Liron Pantanowitz and colleagues at Baystate Medical Center, Tufts University School of Medicine.

Abstract: With the introduction of digital imaging, pathology is undergoing a digital transformation. In the field of cytology, digital images are being used for telecytology, automated screening of Pap test slides, training and education (e.g. online digital atlases), and proficiency testing. To date, there has been no systematic review on the impact of digital imaging on the practice of cytopathology. This article critically addresses the emerging role of computer-assisted screening and the application of digital imaging to the field of cytology, including telecytology, virtual microscopy, and the impact of online cytolgy resources. The role of novel diagnostic techniques like image cytometry is also reviewed.

Keywords: Cytology, cytometry, digital image, informatics, Pap test, proficiency testing, screening, telecytology, virtual image

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Pathologist
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Institution:
Our compass for the industry….

1. … from acquisition thru image analysis, to decision support to report
2. … from “off-time” to real-time
3. … from single-modality to multi-modality
4. … from morphology to molecules (…..morphology AND molecules)
5. … from “information” to “diagnostic confidence”

What does that mean for you?

“from pathologist to diagnostician”
Digital Pathology will:

1. Automate standards of care

2. Redefine standards of care
digital pathology
the last missing link in personalized medicine
Futurescape of Pathology