From Good to Great: The Story of Personalized Management of Colorectal Cancer

Khaled Madbouly, MD, PhD, FRCS, FACS, FASCRS, FISUCRS, MBA

Professor of Colorectal Surgery

Department of Surgery

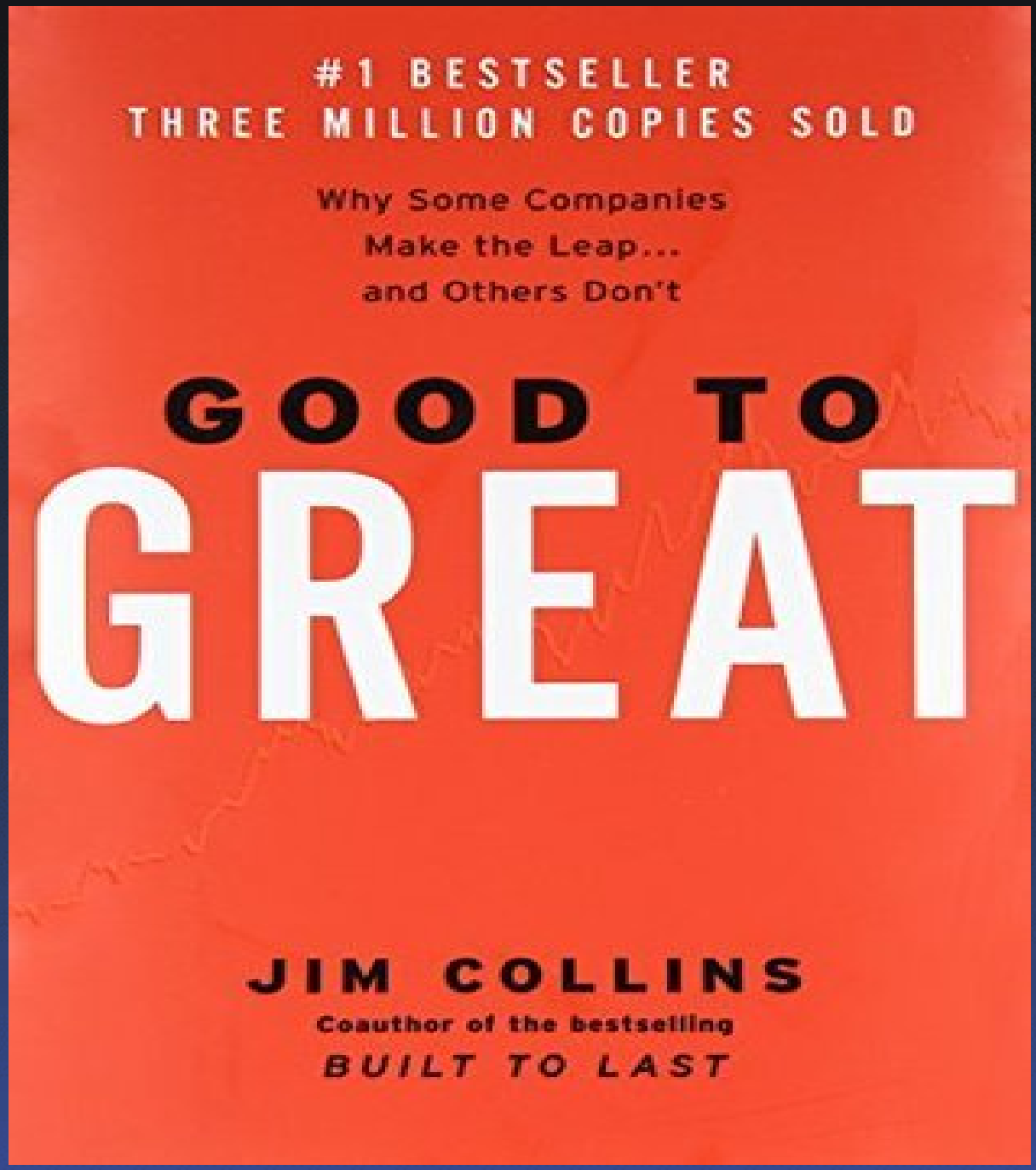
University of Alexandria, EGYPT

A Secretary General of ISUCRS

Secretary General of ESCRS

Vice President of Egyptian Board of Surgery

Vice President of Egyptian Board of Colorectal Surgery


#1 BESTSELLER
THREE MILLION COPIES SOLD
Why Some Companies
Make the Leap...
and Others Don't
GOOD TO
GREAT
JIM COLLINS
Coauthor of the bestselling
BUILT TO LAST

Why some CRC patients respond marvelously to treatment, others don't?

Customize treatment strategies tailored to the need of an individual patient

Personalized Medicine

Personalized Medicine

- What is it?
- Why now?
- Why is the fear?
- Call to Action for colorectal surgeons

Personalized Medicine

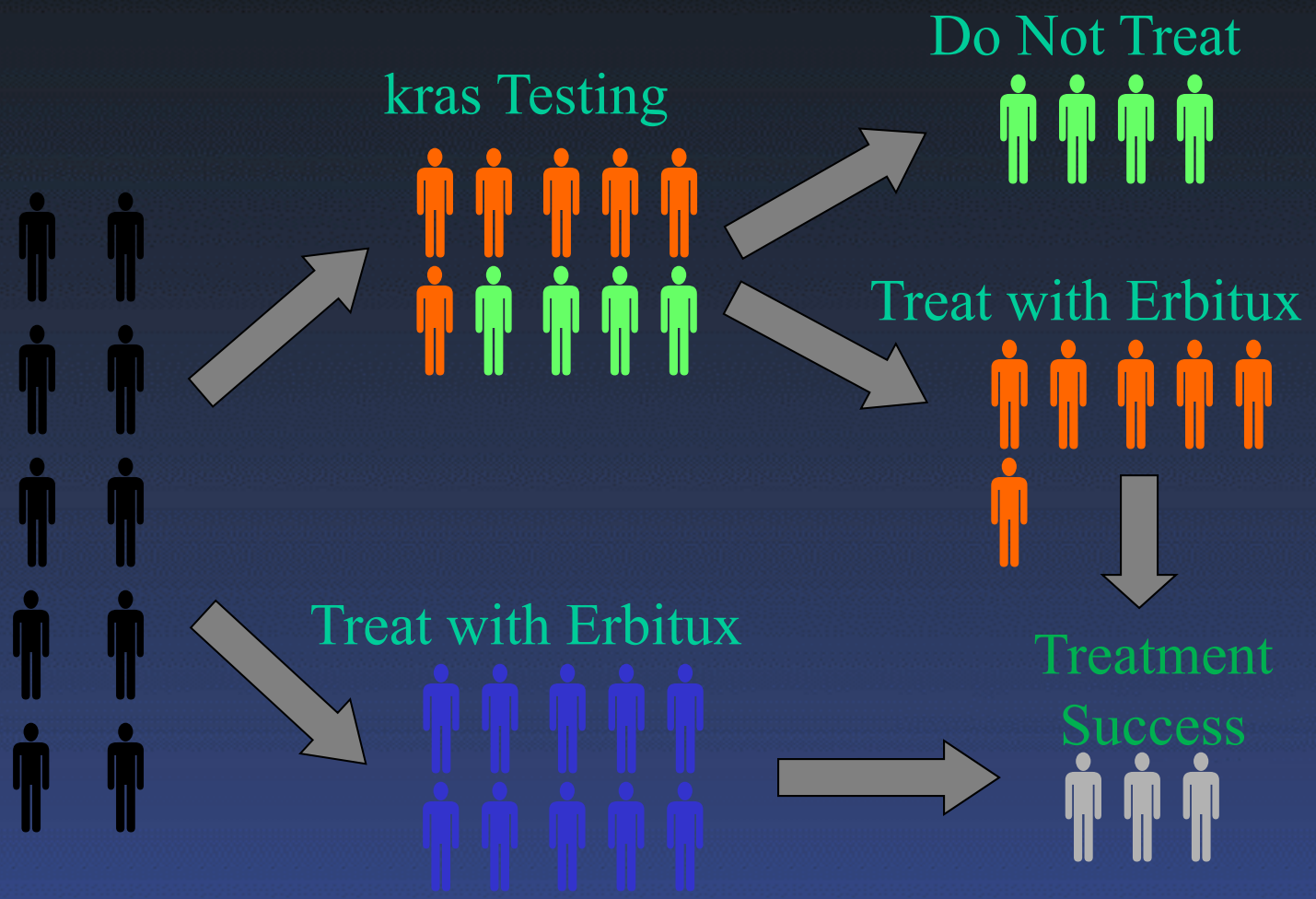
- Customized form of treatment for an individual based on its unique biological attributes
- Expected benefits
  - Accurate and precise way to prevent and cure a disease
  - Avoids unnecessary interventions

Personalized Medicine
Why is it Important?

Diagnosis Save Lives

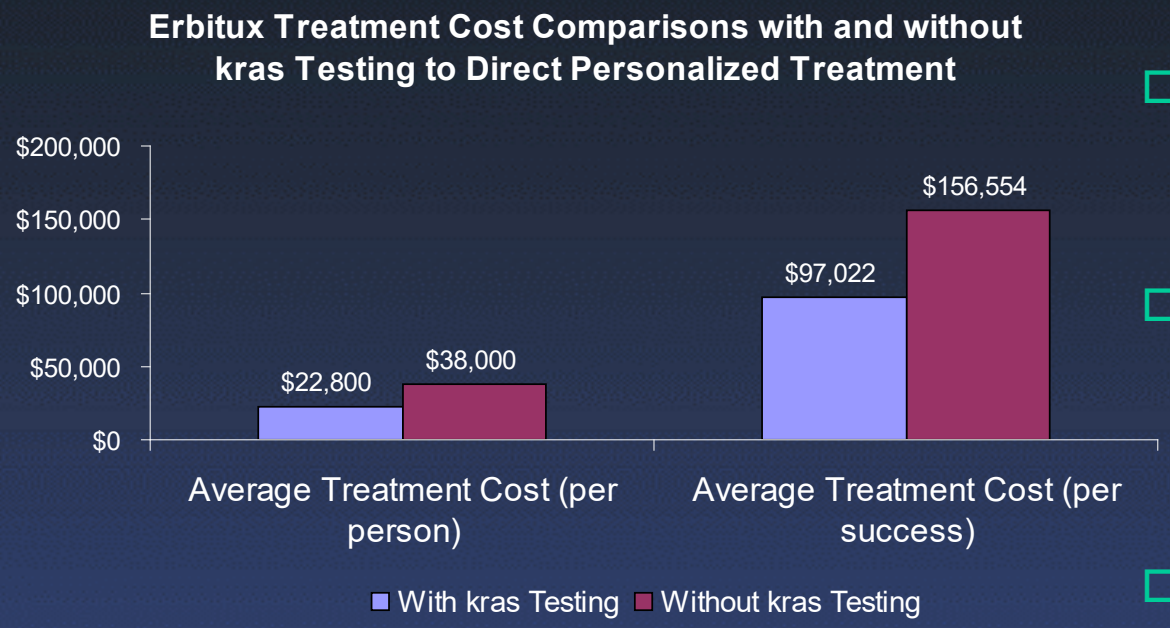
Diagnosis Save Money

Personalized Medicine Reduces Ineffective Treatment in Colon Cancer



Langreth, R. (2008), 'Imclone's Gene Test Battle', Forbes.com, 16May

Personalized Medicine is Cost Effective in Treatment of Colon Cancer



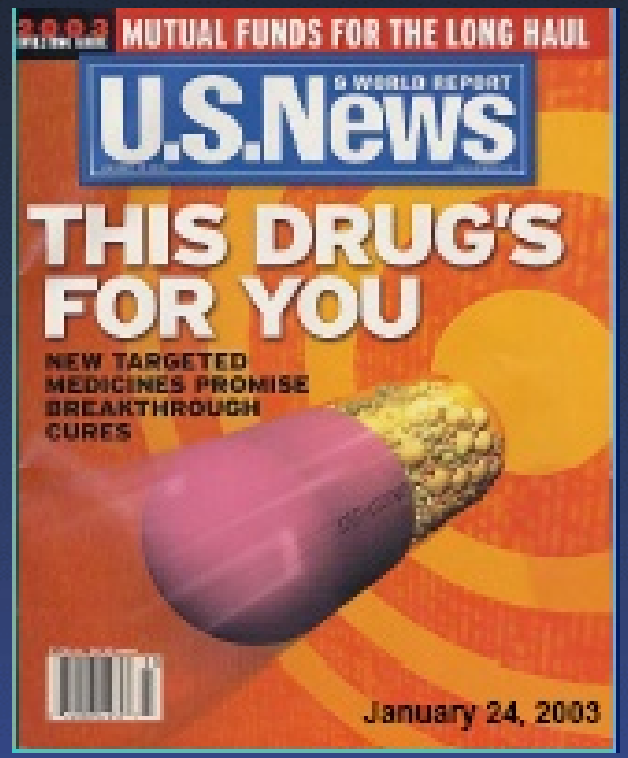
- 60% reduction in cost per success
- 40% of patients spared side effects from ineffective treatment
- Overall success rate is unchanged at 25%

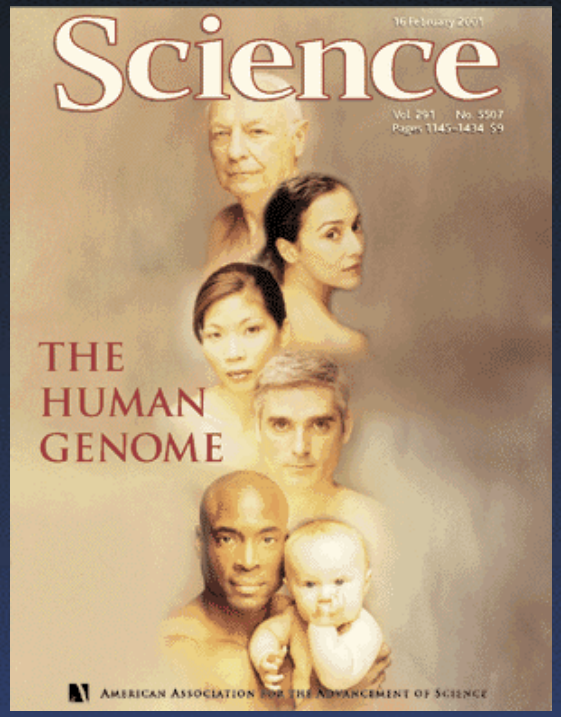
Langreth, R. (2008), 'Imclone's Gene Test Battle', Forbes.com, 16May

Personalized Medicine

- What is it?
- Why now?
- Why is the fear?
- Call to Action

Why Now?
The Human Genome Project





Why Now?
Explosion of the "Omics"

- Proteomics
- Allergenomics
- Bibliomics
- Biomics
- Cardiogenomics
- Cellomics
- Chemogenomics
- Chemoproteomics
- Chromatinomics
- Chromonomics
- Chromosomics
- Combinatorial Peptidomics
- Computational RNomics
- Cryobionomics
- Crystallomics
- Cytochromics
- Cytomics
- Degradomics
- Ecotoxicogenomics
- Eicosanomics
- Embryogenomics
- Enviromics
- Epigenomics
- Epitomics
- Expressomics
- Fluxomics
- Fragmentomics
- Fragonomics
- Etc…

http://www.genomicglossaries.com

Why Now?
Diagnostic Technology Has Improved

Past – Macro Level Testing

Tests differentiated disease from non-disease

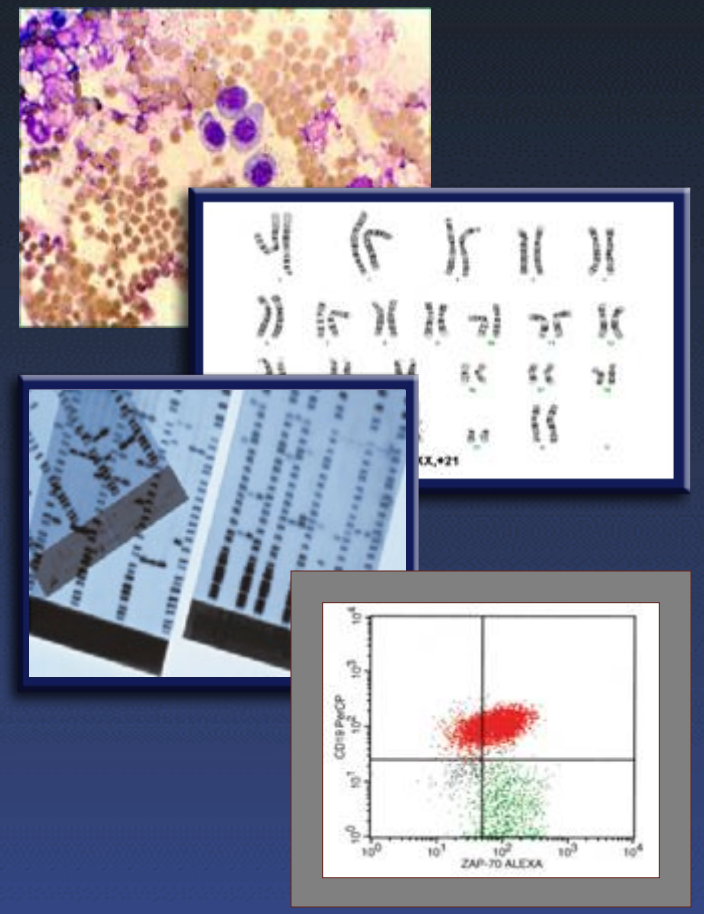
Disease defined by location and size

Today – Molecular Level Testing

Disease defined by individual biology and /or DNA of tumor

Tests to subcategorize disease:

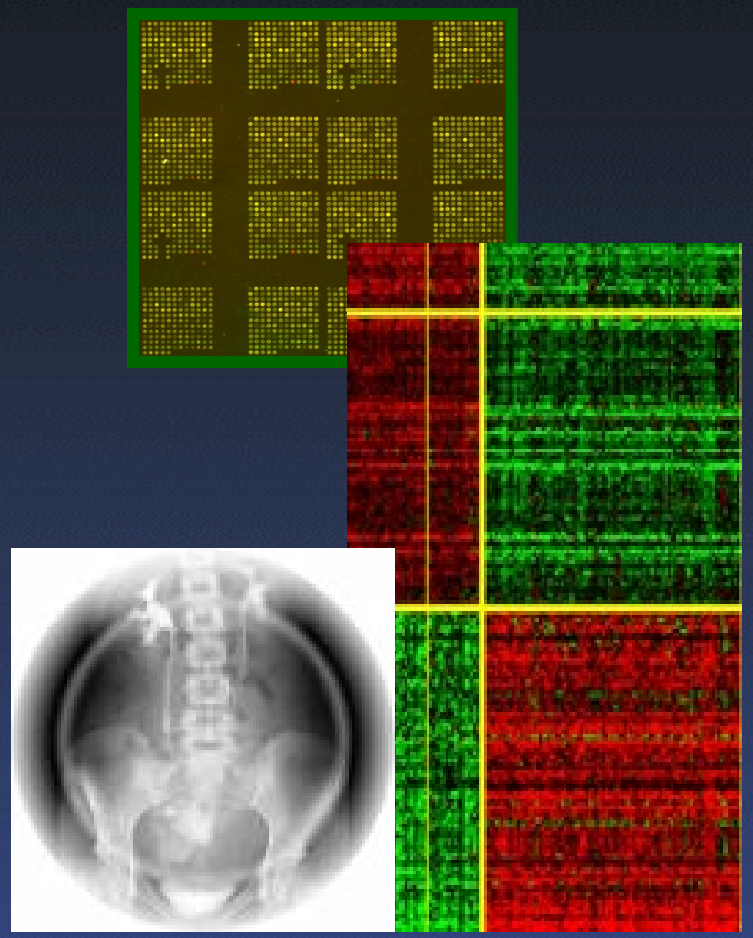
- predict outcomes of specific therapeutic
- screen for adverse events
- monitor disease



Why Now?
Diagnostic Technology Has Improved

Tomorrow – Predictive Testing

- Multiple technology platforms needed for higher analytic validity
- Multi-factorial testing for common, complex diseases
- Multi-gene signatures as standard for cancer
- Increased Use of Diagnostic Imaging



Why Now?
Increased problems from standard care

- Some investigations are deceiving in some patients
- Progression in some cases of rectal cancer while on nCXRT
- 15% second malignancy after nCXRT
- Lack of response to 5-Fu in HNPCC
- Unexpected response after adjuvant chemotherapy

Personalized Medicine

- What is it?
- Why now?
- Why is the fear?
- Call to Action for Pathologists

The Personalized Medicine Timeline
Fear

Payers: Adds to My Cost Without Return

Treating Physicians: Too Prescriptive for Me

Patients: Will I Be Denied Access to New Drugs?

Regulators: How Do We Handle New Complexities?

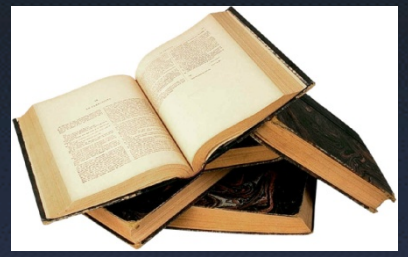
Diagnostics: More Tests With Poor Reimbursement

Pharma: Reduces My Market

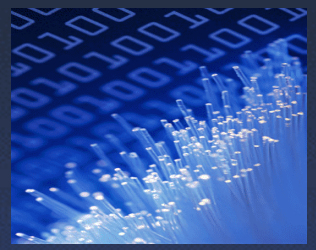
Pathologists: Reduces My Market

Moving From Fear To Acceptance

- Physician Education



- Data are still needed



- Policy – Reimbursement and admins

Move From Fear to Acceptance

- Physician Education
  - Build commitment through education for community physicians
  - Publish new practice guidelines – tests and technologies
- Policies Needed
  - Reimbursement based on value rather than activity
  - Regulatory options that encourage diagnostic and drug combinations

- Embrace "Era of Diagnostics" For Improved Outcomes

The Story of CRC

- 1.6 m cases of CRC and 0.8 m deaths worldwide in 2015
  (Global Burden of Disease Cancer C., 2016)

- Current practice of prevention and therapy of CRC is based on models that presume the population to be homogenous, but the cancer community is increasingly recognizing that a 'one size fits all' model has not been successful

- Heterogeneous nature is acknowledged as a major problem in accurate therapies (Ogino et al., 2012)

The story

- Two main pathways
  - Chromosomal instability (CIN) 85%
  - Microsatellite instability (MSI) 15%
- Molecular pathways used to classify CRC patients and guide treatment regimens

Still need to better customize treatment strategies keeping in view the heterogeneity in every patient

(Lugli, 2015; Sinicrope et al., 2016)

CRC personalized management

- It mostly relies on mutation data from genomics based studies
  - Mutant KRAS didn't respond to EGFR inhibitors was a convincing evidence that not all CRC respond to a drug in the same way (Phipps et al., 2013)
  - BRAF, DNA polymerase influence survival (Zocche et al., 2015)
  - No advantage of adjuvant treatment for MSI patients (NgandSchrag,2010)
  - 25% of MSI exhibited an excellent response to chemotherapy due to a large deletion in the T intronic repeat of HSP110 (Collura et al., 2014)

CRC personalized management

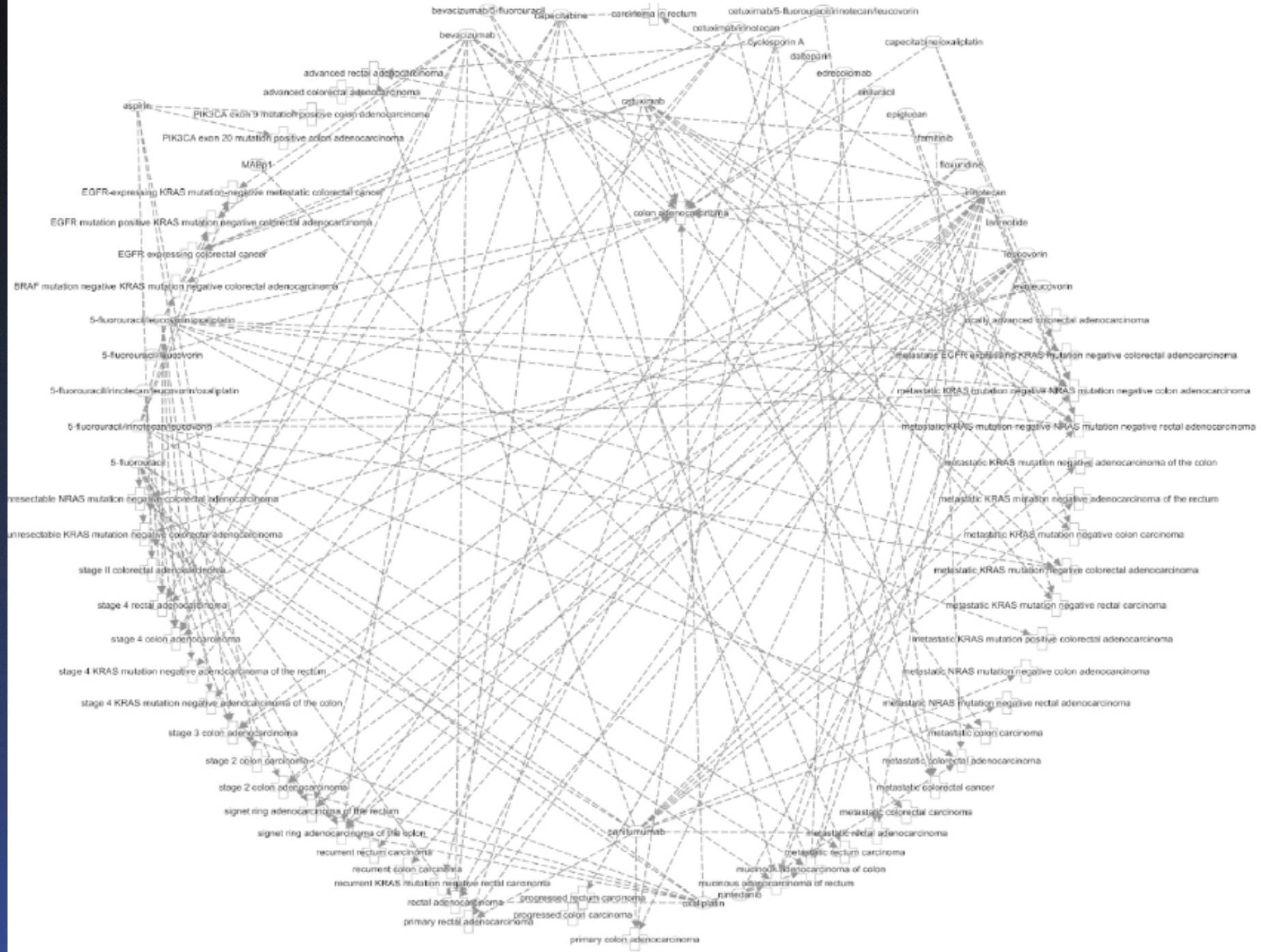
- Genome-wide association studies (GWAS) have identified SNPs associated with the risk of development and progression of CRC and therapeutic responses (Zhu et al., 2012)
- SNPs may have applications for personalized medicine
  - Testing patients for rs396991 SNPs may allow prediction of therapeutic responses to drugs such as cetuximab (Zhang et al., 2007)

(Studies are far from being clinically applicable, as the functional implications of these SNPs are not understood in CRC)

CRC personalized management

- New biomarkers ir classification of CRC patients who would benefit the most from adjuvant chemotherapy at a particular stage (Gangadhar and Schilsky, 2010)

- Large-scale data at the protein and metabolite levels, could be combined with other omics data using integrated models, thus identifying new biomarkers for CRC


bevacizumab/5-fluorouracil
capecitabine
carcinoma in rectum
cetuximab/5-fluorouracil/irinotecan/leucovorin
cetuximab/irinotecan
bevacizumab
cyclosporin A
capecitabine/oxaliplatin
dalteparin
advanced rectal adenocarcinoma
edrecolomab
advanced colorectal adenocarcinoma
aspirin
cetuximab
PIK3CA exon 9 mutation positive colon adenocarcinoma
epiglucan
PIK3CA exon 20 mutation positive colon adenocarcinoma
imatinib
MAPp1
fluorouracil
EGFR-expressing KRAS mutation-negative metastatic colorectal cancer
irinotecan
colon adenocarcinoma
EGFR mutation positive KRAS mutation negative colorectal adenocarcinoma
lanreotide
EGFR expressing colorectal cancer
leucovorin
BRAF mutation negative KRAS mutation negative colorectal adenocarcinoma
levoleucovorin
5-fluorouracil/leucovorin/oxaliplatin
locally advanced colorectal adenocarcinoma
5-fluorouracil/leucovorin
metastatic EGFR expressing KRAS mutation negative colorectal adenocarcinoma
5-fluorouracil/irinotecan/leucovorin/oxaliplatin
metastatic KRAS mutation negative NRAS mutation negative colon adenocarcinoma
5-fluorouracil/irinotecan/leucovorin
metastatic KRAS mutation negative NRAS mutation negative rectal adenocarcinoma
5-fluorouracil
metastatic KRAS mutation negative adenocarcinoma of the colon
nresectable NRAS mutation negative colorectal adenocarcinoma
metastatic KRAS mutation negative adenocarcinoma of the rectum
unresectable KRAS mutation negative colorectal adenocarcinoma
metastatic KRAS mutation negative colon carcinoma
stage II colorectal adenocarcinoma
metastatic KRAS mutation negative colorectal adenocarcinoma
stage 4 rectal adenocarcinoma
metastatic KRAS mutation negative rectal carcinoma
stage 4 colon adenocarcinoma
metastatic KRAS mutation positive colorectal adenocarcinoma
stage 4 KRAS mutation negative adenocarcinoma of the rectum
metastatic NRAS mutation negative colon adenocarcinoma
stage 4 KRAS mutation negative adenocarcinoma of the colon
metastatic NRAS mutation negative rectal adenocarcinoma
stage 3 colon adenocarcinoma
metastatic colon carcinoma
stage 2 colon carcinoma
metastatic colorectal adenocarcinoma
stage 2 colon adenocarcinoma
metastatic colorectal cancer
signet ring adenocarcinoma of the rectum
metastatic colorectal carcinoma
panitumumab
signet ring adenocarcinoma of the colon
metastatic rectal adenocarcinoma
recurrent rectum carcinoma
metastatic rectum carcinoma
recurrent colon carcinoma
mucinous adenocarcinoma of colon
recurrent KRAS mutation negative rectal carcinoma
mucinous adenocarcinoma of rectum
progressed rectum carcinoma
nimotuzumab
rectal adenocarcinoma
oxaliplatin
progressed colon carcinoma
primary rectal adenocarcinoma
primary colon adenocarcinoma

Challenges for personalized CRC management

- Strengths of personalized medicine is undermined by the lack of inclusion of genetically diverse human populations

  (Ramos et al., 2012)

- There are many statistical challenges that hamper patient studies with small numbers
- Personalized medicine would require data analysis to be robust enough to a level where each patient becomes a separate class and the predictions can be made with the utmost accuracy

Challenges for personalized CRC management

- Hard to develop computational tools to integrate multi omics data that can recapitulate the changing dynamics of underlying biology of the CRC patients
- Large difference in individuals requires the use of a patient's own baseline healthy data as a'control'

(Hood and Friend, 2011)

- In CRC, the challenge of personalized medicine is to match the patient with the effective drug regimen

Challenges for personalized CRC management

- Therapeutic regimens for distant metastasis (e.g. 5-FU + Leucovorin +Oxaliplatin/Irinotecan; FOLFOX/FOLFIRI) require further customization to minimize toxicity
- Variation in response to the therapeutic regimens could be due to the underlying differences in molecular characteristics of CRC patients

Call for action

- The future success depends on two major factors:
  - Technological advances to generate high-quality, holistic protein and metabolite level data
  - An ability to integrate data across different hierarchical levels of biological information (DNA, RNA, protein and metabolites) and at different levels of organization (cell, tissue and organ)

Personalized medicine in CRC

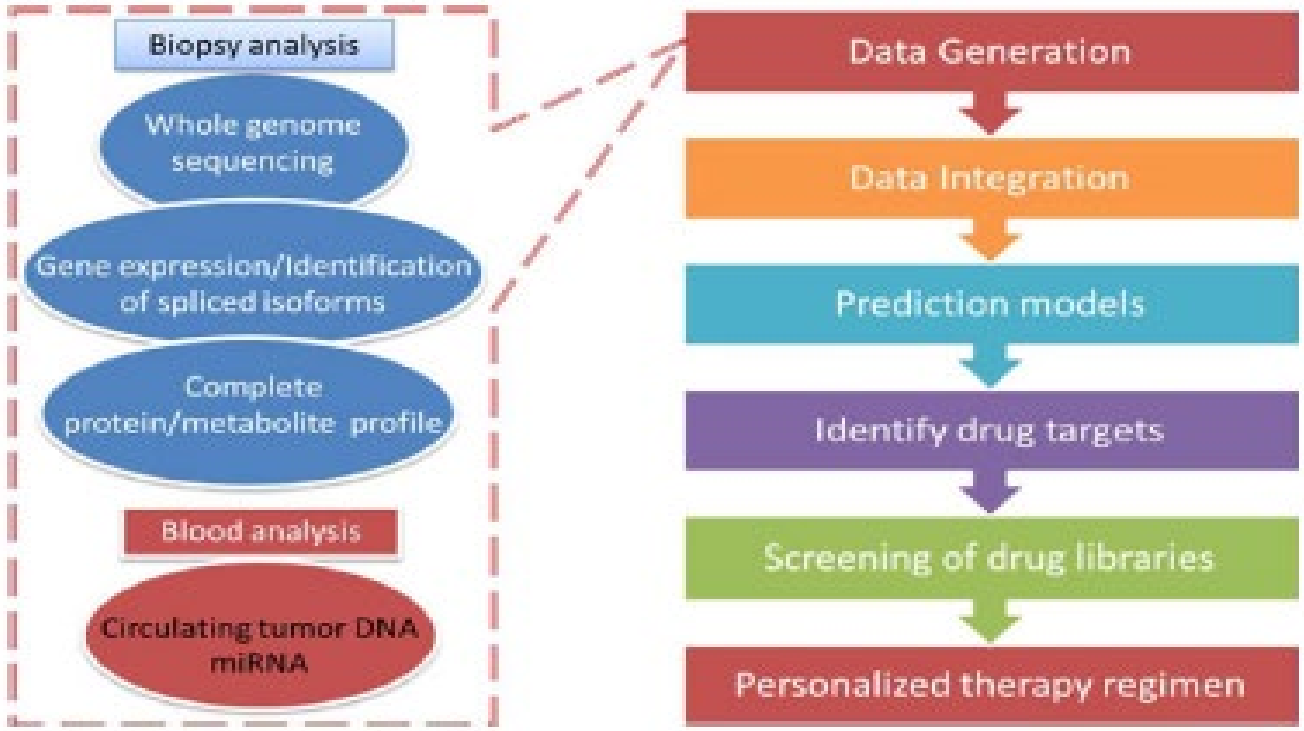


Fig. 3. Workflow for personalized medicine in colorectal cancer.

Critical Reviews in Oncology / Hematology 118 (2017) 70–78

Conclusion

- The current management of CRC is challenged by the extensive heterogeneity in this disease, suggesting that this is a complex disease that could benefit from the implementation of a personalized medicine approach
- Impressive increase in our ability to generate omics data from nucleic acids, and there are expectations that this will also be possible for proteins and metabolites

Conclusion

- 'one size fits all' model has not been successful
- Although there are still challenges to be met, such as data integration, building prediction models and implementing patient-specific customized solutions for CRC therapy, we are optimistic about the success of personalized medicine for this disease

Thank you