

# Genomics and cancer a moving landscape

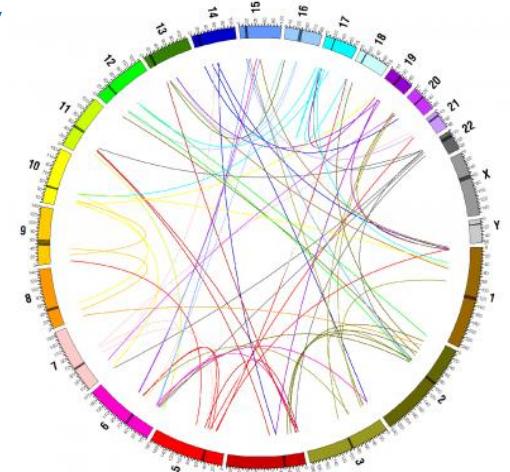
Alla L Lapidus, Ph.D.

Associate Professor  
Fox Chase Cancer Center

# Start of the Genomic Medicine Era

Human genome took about 23 years and several billion dollars to start the project and to publish the draft sequence (finishing is still in progress).

But this is not the end of the story  
This is only the beginning



Nature, 2009

# **“REVOLUTIONARY GENOME SEQUENCING TECHNOLOGIES THE \$1000 GENOME”**

(Department of Health and Human Services (DHHS))

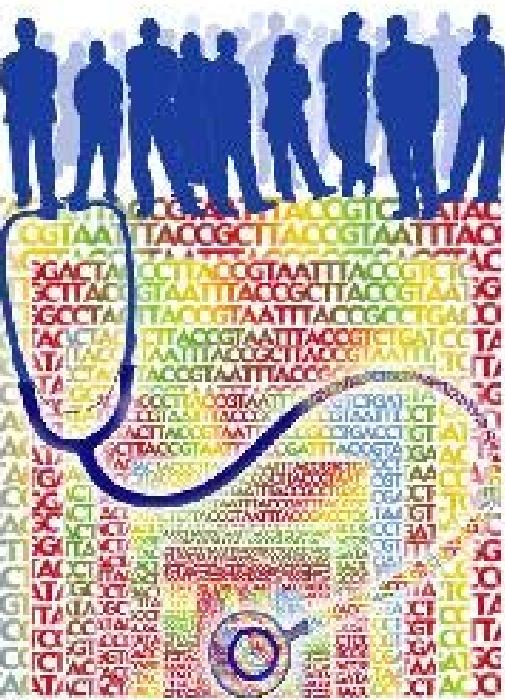
2004 - develop novel technologies that will enable extremely low-cost, high quality DNA sequencing

2009 - the cost to sequence an entire individual human genome to be \$1,000 by the end of 2009 and the time required for sequencing less than one week

*we are not there yet but very close – it is about \$5000 these days*

2012 - The NIH plans to award \$5.7 million in funding for research projects that explore ways to use genome sequencing in clinical care, and \$800,000 to fund a coordinating center to support these studies.

# Clinical sequencing



But even at this stage DNA sequencing is already a very attractive tool that can be used not only for the purpose of conducting research, but also for clinical studies and, most importantly, to improve the quality of clinical diagnosis and the selection of treatments for individual patients.

## CANCER BIOLOGY

### Sequencing guides cancer treatment



**HIGHLY READ**  
on genome-  
biology.com in  
the last 30 days

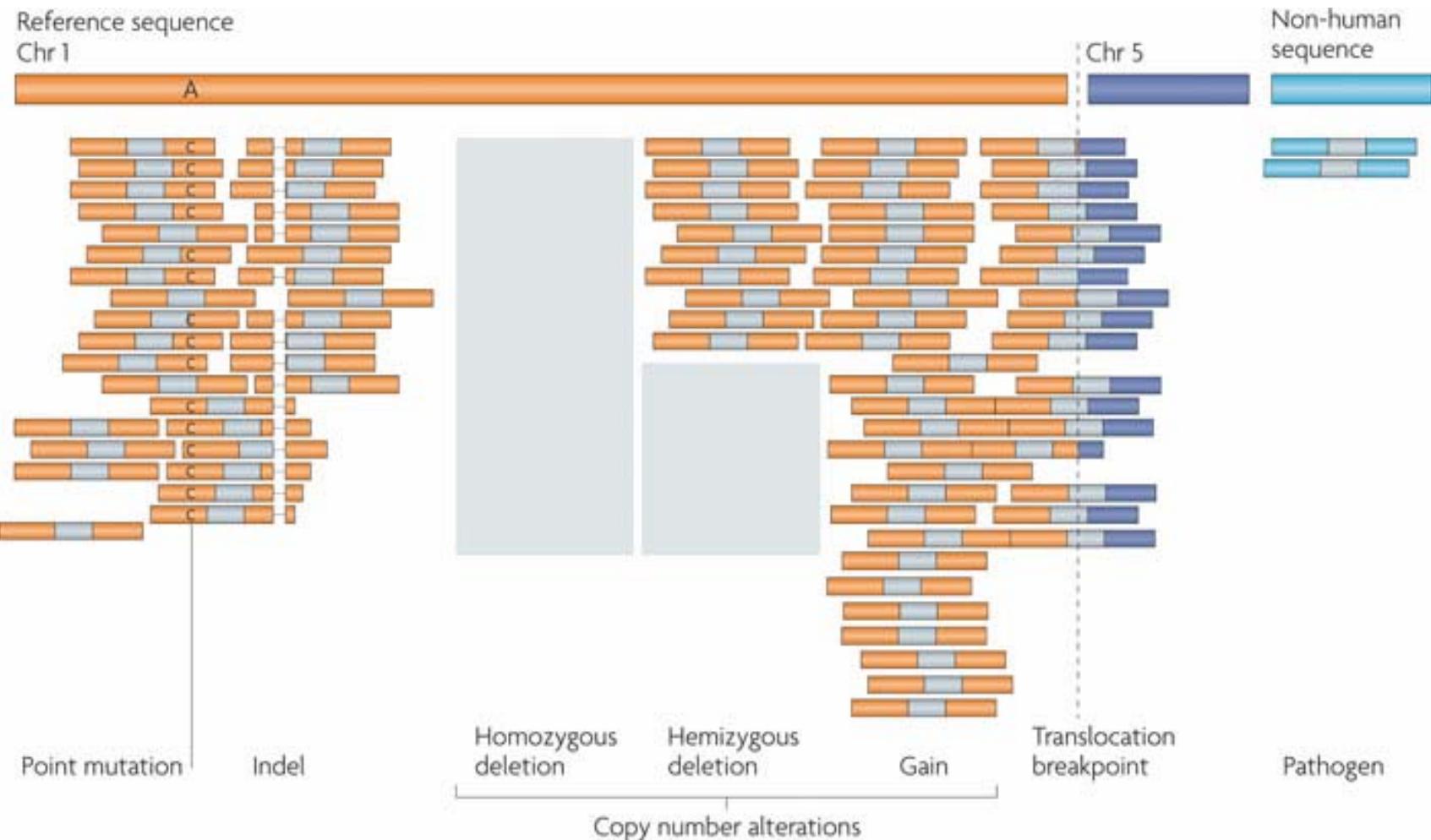
The full genome sequence of a rare tongue tumour has allowed physicians to draw up a personalized treatment plan where no established protocol existed.

A 78-year-old patient had his cancer sequenced after initial treatments failed to slow tumour growth, which had spread to his lungs. When Steven Jones of the British Columbia Cancer Agency in Vancouver, Canada, and his colleagues analysed the sequence and compared it with that of his normal cells, they determined that tumour growth was probably driven by overexpression of a cancer-promoting gene called *RET*.

A combination of drugs that target *RET* held back the cancer for seven months, until the tumours became drug-resistant. The team sequenced the cancer again and identified new mutations that had activated the AKT and MAPK pathways, which are often upregulated in cancer. The results provide a snapshot of how tumours evolve to evade treatment.

*Genome Biol.* 11, R82 (2010)

# Cancer is a disease of genome alterations. Which alterations can be detected:



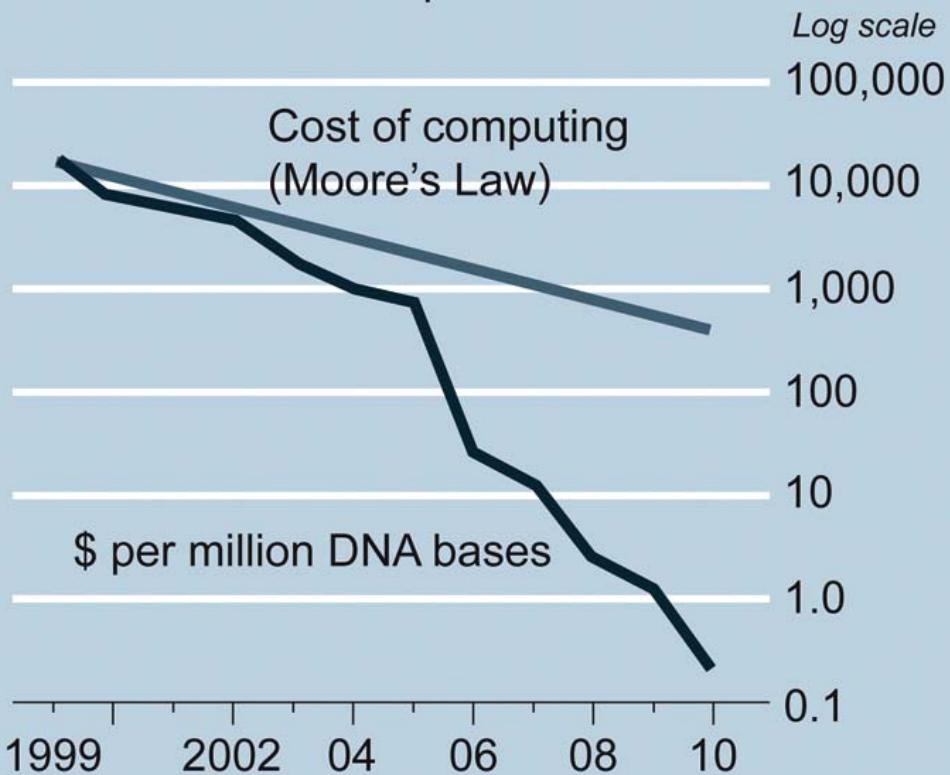
# Cost of computing vs sequencing cost

**Moore's law: computers double in power roughly every two years—an increase of more than 30 times over the course of a decade, with reductions in cost.**

(Moore's law describes a long-term trend in the history of computing hardware. The number of transistors that can be placed inexpensively on an integrated circuit has doubled approximately every two years. The trend has continued for more than half a century and is not expected to stop until 2015 or later.)

## Baseline information

Cost of genome sequencing compared with Moore's Law for computers



Source: Broad Institute

# A map of human genome variation from population-scale sequencing

The 1000 Genomes Project Consortium\*

28 OCTOBER 2010 | VOL 467 |  
NATURE | 1061

Production group

People in different aspects of data analysis

Leena Peltonen<sup>1</sup>, Alan J. Schaffner<sup>2,3</sup>, Stephen L. Arbustamentals<sup>2</sup>, Jun Wang<sup>2,23</sup>, Richard K. Wilson<sup>17</sup>

Production group: Baylor College of Medicine Richard A. Gibbs<sup>14</sup> (Principal Investigator), David Deiros<sup>14</sup>, Mike Metzker<sup>14</sup>, Donna Muzny<sup>14</sup>, Jeff Reid<sup>14</sup>, David Wheeler<sup>17</sup>, BGI-Shenzhen Jun Wang<sup>2,23</sup> (Principal Investigator), Jinghang Li<sup>2,23</sup>, Min Jan<sup>22</sup>, Guoping Li<sup>2,23</sup>, Ruiqiang Li<sup>2,23</sup>, Huijing Liang<sup>2,23</sup>, Geng Tian<sup>22</sup>, Bo Wang<sup>2,23</sup>, Jun Wang<sup>2,23</sup>, Wei Wang<sup>2,23</sup>, Huamming Yang<sup>2,23</sup>, Xueqing Zhang<sup>2,23</sup>, Huisong Zheng<sup>2,23</sup>, Broad Institute of MIT and Harvard Eric S. Lander<sup>15</sup> (Principal Investigator), David L. Altshuler<sup>24</sup>, Lauren Ambrogio<sup>2</sup>, Toby Bloom<sup>2</sup>, Krishan Cibulskis<sup>2</sup>, Tim J. Fennell<sup>2</sup>, Stacey B. Gabriel<sup>2</sup> (Co-Chair), David B. Jaffe<sup>2</sup>, Erica Shaffer<sup>2</sup>, Carrie L. Sougnez<sup>2</sup>, Illumina David R. Bentley<sup>6</sup> (Principal Investigator), Niall Gormley<sup>6</sup>, Sean Humphrys<sup>6</sup>, Zoya Kingsbury<sup>6</sup>, Paula Koko-Gonzales<sup>6</sup>, Jennifer Stone<sup>6</sup>, Life Technologies Kevin J. McKernan<sup>1</sup> (Principal Investigator), Gina L. Costa<sup>6</sup>, Jeffry Ichikawa<sup>6</sup>, Clarence C. Lee<sup>24</sup>, Max Planck Institute for Molecular Genetics Ralf Sudarshan<sup>16</sup> (Project Leader), Hans Lehrach<sup>16</sup> (Principal Investigator), Tatiana A. Borodina<sup>16</sup>, Andreas Dah<sup>25</sup>, Aleksey N. Davydov<sup>26</sup>, Peter Marquardt<sup>16</sup>, Wilfried Mielke<sup>16</sup>, Philip Rosenblatt<sup>26</sup>, Stefan Schreiber<sup>26</sup>, Aleksey V. Soldatov<sup>16</sup>, Bernd Timmermann<sup>16</sup>, Maria Tolzmann<sup>16</sup>, Roche Applied Science Michael Egholm<sup>12</sup> (Principal Investigator), Jason Alford<sup>17</sup>, Dana Aszkenasy<sup>27</sup>, Said Attya<sup>27</sup>, Melissa Bachori<sup>27</sup>, Bill Buglione<sup>27</sup>, Adam Butke<sup>27</sup>, Amanda Caprio<sup>27</sup>, Christopher Colone<sup>27</sup>, Shaura Clark<sup>27</sup>, David Connors<sup>27</sup>, Brian Desany<sup>27</sup>, Lisa Gu<sup>27</sup>, Lorri Giucione<sup>27</sup>, Calvin Kao<sup>27</sup>, Andrew Kebede<sup>27</sup>, Jennifer Knollton<sup>27</sup>, Matthew Laskerque<sup>27</sup>, Louise McDade<sup>27</sup>, Craig Meissner<sup>27</sup>, Melissa Minderman<sup>27</sup>, Anne Nawrocki<sup>27</sup>, Faheem Nazir<sup>27</sup>, Kristen Pareja<sup>27</sup>, Rani Ramanathan<sup>27</sup>, David Riches<sup>27</sup>, Wannmin Song<sup>27</sup>, Cynthia Turcotte<sup>27</sup>, Shally Wang<sup>27</sup>, Washington University in St Louis Elaine R. Mardis<sup>27</sup> (Co-Chair), Co-Principal Investigator, Robert K. Wilson<sup>27</sup> (Co-Principal Investigator), David Dooling<sup>17</sup>, Lucinda Fulton<sup>17</sup>, Robert Fulton<sup>17</sup>, George Winstock<sup>17</sup>, Wellcome Trust Sanger Institute Richard M. Durbin<sup>1</sup> (Principal Investigator), John Burton<sup>1</sup>, David M. Carter<sup>1</sup>, Carol Churcher<sup>1</sup>, Alison Coffey<sup>1</sup>, Anthony Cox<sup>1</sup>, Anna Palotie<sup>1,28</sup>, Michael Quail<sup>1</sup>, Tessa Skelley<sup>1</sup>, James Stalker<sup>1</sup>, Harold P. Swerdlow<sup>1</sup>, Daniel Turner<sup>1</sup>.

Analysis group: Baylor College of Medicine Richard A. Gibbs<sup>14</sup> (Principal Investigator), David Wheeler<sup>14</sup>, Matthew Bainbridge<sup>14</sup>, Danny Challis<sup>14</sup>, Anika Sabo<sup>14</sup>, Full Yu<sup>14</sup>, Li Yu<sup>14</sup>, BGI-Shenzhen Jun Wang<sup>2,23</sup> (Principal Investigator), Xiaodong Fan<sup>2,23</sup>, Xiaosen Guo<sup>2,23</sup>, Xuguang Li<sup>2,23</sup>, Yingru Li<sup>2,23</sup>, Ruibang Luo<sup>2,23</sup>, Shushuai Tai<sup>2,23</sup>, Xionglong Wu<sup>2,23</sup>, Han-Jeng Cheng<sup>2,23</sup>, Yan Zhou<sup>2,23</sup>, Guoping Li<sup>2,23</sup>, Jian Wang<sup>2,23</sup>, Huang Yang<sup>2,23</sup>, Boston College Gabor T. Martin<sup>10</sup> (Principal Investigator), Erik P. Garrison<sup>10</sup>, Yichun Huang<sup>10</sup>, Amit Indap<sup>10</sup>, Deniz Kara<sup>10</sup>, Wan-Ping Lee<sup>10</sup>, Wen-Feng Leong<sup>10</sup>, Aaron R. Quinlan<sup>12</sup>, Chip Stewart<sup>12</sup>, Michael P. Stromberg<sup>12</sup>, Alastair N. Ward<sup>12</sup>, Ilia Tsiantis<sup>12</sup>, Wu<sup>2,23</sup>, Brigham and Women's Hospital Charles Lee<sup>29</sup> (Principal Investigator), John E. Mills<sup>34</sup>, Xinghua Shi<sup>34</sup>, Broad Institute of MIT and Harvard Mark J. Daly<sup>34</sup> (Principal Investigator), Mark A. DePristo<sup>34</sup> (Project Leader), David L. Altmire<sup>24</sup>, Aaron D. Eskin<sup>34</sup>, Eric Banks<sup>34</sup>, Toby Bloom<sup>2</sup>, Brian L. Browning<sup>2</sup>, Kristian Cibulskis<sup>2</sup>, Tim J. Fennell<sup>2</sup>, Kraig V. Germino<sup>34</sup>, Shamra N. Grossman<sup>34</sup>, Robert E. Handaker<sup>2</sup>, Matt Hama<sup>2</sup>, Cole Hart<sup>2</sup>, David B. Jaffe<sup>2</sup>, Andrew M. Kennedy<sup>34</sup>, Joshua M. Kern<sup>2</sup>, Heng Li<sup>2</sup>, Jared R. Maguire<sup>2</sup>, Steven A. McCarroll<sup>2</sup>, Aaron McFern<sup>2</sup>, James C. Nemes<sup>2</sup>, Anthony A. Philippakis<sup>34</sup>, Ryan E. Poplin<sup>2</sup>, Alkes Price<sup>37</sup>, Manuel A. Rivas<sup>34</sup>, Pauli S. Sabeti<sup>34</sup>, Stephen F. Schaffner<sup>2</sup>, Erica Shaffer<sup>2</sup>, Ilya A. Shlyakhter<sup>34</sup>, Cardiff University, The Human Genome Mutation Database David N. Cooper<sup>10</sup> (Principal Investigator), Edward V. Ball<sup>10</sup>, Matthew Mort<sup>10</sup>, Andrew D. Phillips<sup>10</sup>, Peter D. Stenson<sup>10</sup>, Cold Spring Harbor Laboratory Jonathan Sels<sup>29</sup> (Principal Investigator), Vladimir Makarov<sup>46</sup>, Kenny Ye<sup>1</sup>, Seungtae C. Yoon<sup>42</sup>, Cornell and Stanford Universities Carlos D. Bustamante<sup>43</sup> (Co-Principal Investigator), Andrew G. Clark<sup>43</sup> (Principal Investigator), Adam Boyko<sup>43</sup>, Jeremiah Degenhardt<sup>8</sup>, Simon Gravell<sup>43</sup>, Ryan N. Gutierrez<sup>44</sup>, Mark Kaganovich<sup>43</sup>, Alon Keinan<sup>43</sup>, Phil Lacleure<sup>43</sup>, Xin Ma<sup>43</sup>, Andy Reynolds<sup>43</sup>, European Bioinformatics Institute Laura Clarke<sup>13</sup> (Project Leader), Paul Flicek<sup>13</sup> (Co-Chair), Richard E. Smith<sup>13</sup>, Xiangyun Zheng-Bradley<sup>13</sup>, European Molecular Biology Laboratory Jan O. Korber<sup>45</sup>, Illumina Sean Humphrys<sup>6</sup> (Project Leader), R. Keira Cheetham<sup>6</sup>, Michael Eberle<sup>6</sup>, Scott Kahn<sup>6</sup>, Lia Murray<sup>6</sup>, Leiden University Medical Center Kai Ye<sup>46</sup>, Life Technologies Francisco M. De La Vega<sup>10</sup> (Principal Investigator), Yusuf Fu<sup>10</sup>, Heather E. Peckham<sup>24</sup>, Yongming A. Sun<sup>10</sup>, Louisiana State University Mark A. Batzer<sup>10</sup> (Principal Investigator), Miriam K. Konetz<sup>47</sup>, Jenilyn A. Walker<sup>47</sup>, US National Institutes of Health Chunlin Xie<sup>21</sup>, Oxford University Zimin Xie<sup>21</sup>, Roche Applied Science Brian Desany<sup>27</sup>, University of Michigan Tom Blackwell<sup>27</sup> (Project Leader), Matthew Snyder<sup>1</sup>, University of Utah Jinchuan Xing<sup>29</sup>, University of Washington Evan E. Eichler<sup>27</sup> (Co-Chair) (Principal Investigator), Gozde Aksay<sup>27</sup>, Can Akhan<sup>27</sup>, Iman Hajirasouli<sup>27</sup>, Fereyoud Hormozdi<sup>27</sup>, Jeffrey M. Kidd<sup>19,48</sup>, Washington University in St Louis Kein Chen<sup>17</sup>, Asif Chinnaiya<sup>17</sup>, Li Ding<sup>17</sup>, Mike D. McLellan<sup>17</sup>, John W. Wallace<sup>17</sup>, Wellcome Trust Sanger Institute Matti Huru<sup>1</sup> (Co-Chair) (Principal Investigator), Donald F. Conrad<sup>1</sup>, Klaudia Walter<sup>1</sup>, Yujun Zhang<sup>1</sup>, Yale and Stanford Universities Mark B. Gerstein<sup>6,56</sup> (Co-Principal Investigator), Michael Snyder<sup>43</sup> (Co-Principal Investigator), Alexej Abzoy<sup>63</sup>, Jiang Du<sup>63</sup>, Fabian Gruber<sup>63</sup>, Rajini Haraksingh<sup>63</sup>, Justin Jee<sup>63</sup>, Edita Khrurans<sup>63</sup>, Hugo Y. K. Lam<sup>43</sup>, Jing Zheng<sup>63</sup>, Ximeng Jasmine Mu<sup>63</sup>, Alexander E. Urban<sup>48,63</sup>, Zhengdong Zhang<sup>63</sup>.

Beta pilot group: Baylor College of Medicine Richard A. Gibbs<sup>14</sup> (Co-Chair) (Principal Investigator), Matthew Bainbridge<sup>14</sup>, Danny Challis<sup>14</sup>, Christian Costa<sup>14</sup>, Huyen Dinh<sup>14</sup>, Christine Kovari<sup>14</sup>, Sandy Lee<sup>14</sup>, Donna Muzny<sup>14</sup>, Lynne Nuzetelli<sup>14</sup>, Jeff Reid<sup>14</sup>, Aniko Sabo<sup>14</sup>, Full Yu<sup>14</sup>, Jin Yu<sup>14</sup>, Boston College Gabor T. Martin<sup>10</sup> (Co-Chair) (Principal Investigator), Erik P. Garrison<sup>10</sup>, Amit Indap<sup>10</sup>, Wen-Feng Leong<sup>10</sup>, Aaron R. Quinlan<sup>12</sup>, Chip Stewart<sup>12</sup>, Alastair N. Ward<sup>12</sup>, Jiantao Wu<sup>12</sup>, Broad Institute of MIT and Harvard Kristin Cibulskis<sup>2</sup>, Raskas Indap<sup>2</sup>, Tim J. Fennell<sup>2</sup>, Stacey B. Gabriel<sup>2</sup>, Kiran V. Germino<sup>2</sup>, Chris Hart<sup>2</sup>, Erica Shaffer<sup>2</sup>, Carrie L. Sougnez<sup>2</sup>, Jane Wilkinson<sup>2</sup>, Cornell and Stanford Universities Andrew B. Clark<sup>43</sup> (Co-Principal Investigator), Simon Gravell<sup>43</sup>, Fabian Gruber<sup>43</sup>, European Bioinformatics Institute Laura Clarke<sup>13</sup> (Project Leader), Paul Flicek<sup>13</sup> (Principal Investigator), Richard E. Smith<sup>13</sup>, Xiangyun Zheng-Bradley<sup>13</sup>, US National Institutes of Health Stephen T. Sherry<sup>21</sup> (Principal Investigator), Horacio Kauri<sup>21</sup>, Justin E. Paschall<sup>21</sup>, Martin F. Shumway<sup>21</sup>, Chunlin Xie<sup>21</sup>, Oxford University Gil A. McEwan<sup>11,18</sup>, University of California, Santa Cruz J. Katzenbach<sup>29</sup>, University of Michigan Gong Yu R. Abecasis<sup>2</sup> (Principal Investigator), Tom Blasewitz<sup>2</sup>, Washington University in St Louis Elsie Wendl<sup>2</sup> (Principal Investigator), David Dooling<sup>17</sup>, Lucinda Fulton<sup>17</sup>, John Fulton<sup>17</sup>, Daniel C. Koboldt<sup>17</sup>, Wellcome Trust Sanger Institute Richard M. Durbin<sup>1</sup> (Principal Investigator), Sendurana Subramanian<sup>1</sup>, Anna Coffey<sup>1</sup>, Thomas M. Keane<sup>1</sup>, Daniel G. MacArthur<sup>1</sup>, Adrien Marullo<sup>1,28</sup>, Carol Scott<sup>1</sup>, James Stalker<sup>1</sup>, Chris Tyler-Smith<sup>1</sup>, Yale University Mark B. Gerstein<sup>1</sup> (Principal Investigator), Suganthi Balasubramanian<sup>1</sup>.

Samples and ELIS group Aravinda Chakravarthy<sup>1</sup> (Co-Chair), Bartha M. Knoppers<sup>13</sup> (Co-Chair), Leena Peltonen<sup>1</sup>, (Co-Chair), Gonçalo R. Abecasis<sup>2</sup>, Carlos D. Bustamante<sup>43</sup>, Nedra Ghosh<sup>29</sup>, Richard A. Gibbs<sup>14</sup>, Lynn Jordan<sup>27</sup>, Jane S. Kaye<sup>70</sup>, Alastair Kent<sup>71</sup>, Taisha Li<sup>22</sup>, Amy L. McGuire<sup>72</sup>, Gill A. McVean<sup>11,18</sup>, Pilar N. Osorio<sup>73</sup>, Charles N. Rotimi<sup>74</sup>, Yeyang Su<sup>22</sup>, Lorraine H. Top<sup>29</sup>, Chris Tyler-Smith<sup>1</sup>.

Scientific management Lisa D. Brooks<sup>75</sup>, Adam L. Felsenfeld<sup>75</sup>, Jean E. McEwen<sup>75</sup>, Asya Abdalla<sup>76</sup>, Christopher R. Juenger<sup>77</sup>, Nicholas C. Clemm<sup>75</sup>, Francis S. Collins<sup>78</sup>, Audrey Duncanson<sup>79</sup>, Eric D. Green<sup>78</sup>, Mark S. Guyer<sup>75</sup>, Jane L. Peterson<sup>75</sup>, Alan J. Schafer<sup>70</sup>.

- wgs of 179 individuals from 4 populations
- 2 mother-father-child trio (high coverage)
- Exome-targeted sequencing of 697 individuals

# Huge need in bioinformatics tools: Simple pipelines/protocols and easy to read reports



Sample sequencing



Data Analysis



Doctors simple life = Hard work for programmers and bioinformatitons

Patients treatment

# Team work to set up cancer sequencing facility



# Routine diagnostics of cancer patients

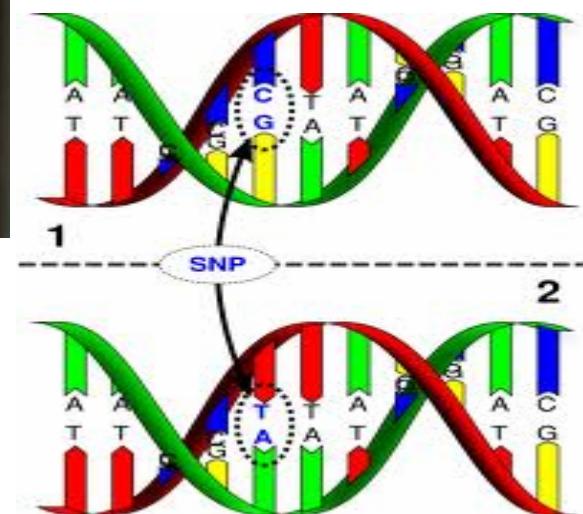
## Step by step plan

- Stage 1 - sequence of panel of well characterized onco-specific genes and gene onco-suppressors
- Stage 2 - Sequence and analysis of all coding regions of the genome (full exome sequence) together with the analysis of gene expression level (transcriptome)
- Stage 3 - Sequence and analysis of the complete genome of each patient

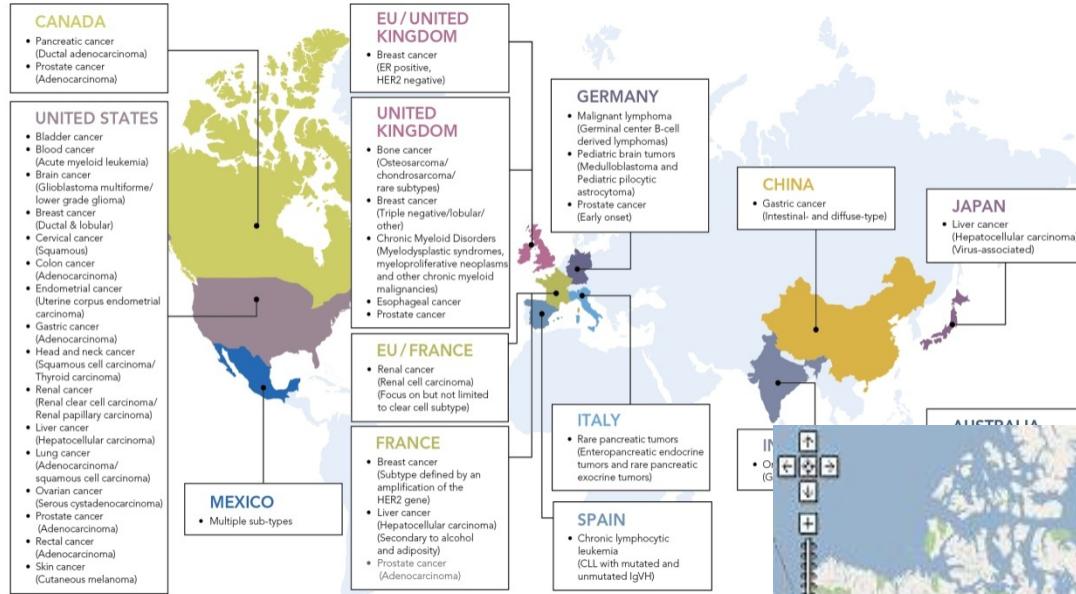
# The ethical, legal, and social issues

- data to be released to the patient
- data release and identifiability
- data that can be released into the public domain
- protection of patient confidentiality
- sharing and understanding data (what to do with all the findings for the individual patient etc.)
- data storage security, confidentiality and reliability
- how long to store data?
- sequencing service cost
- insurance
- .....

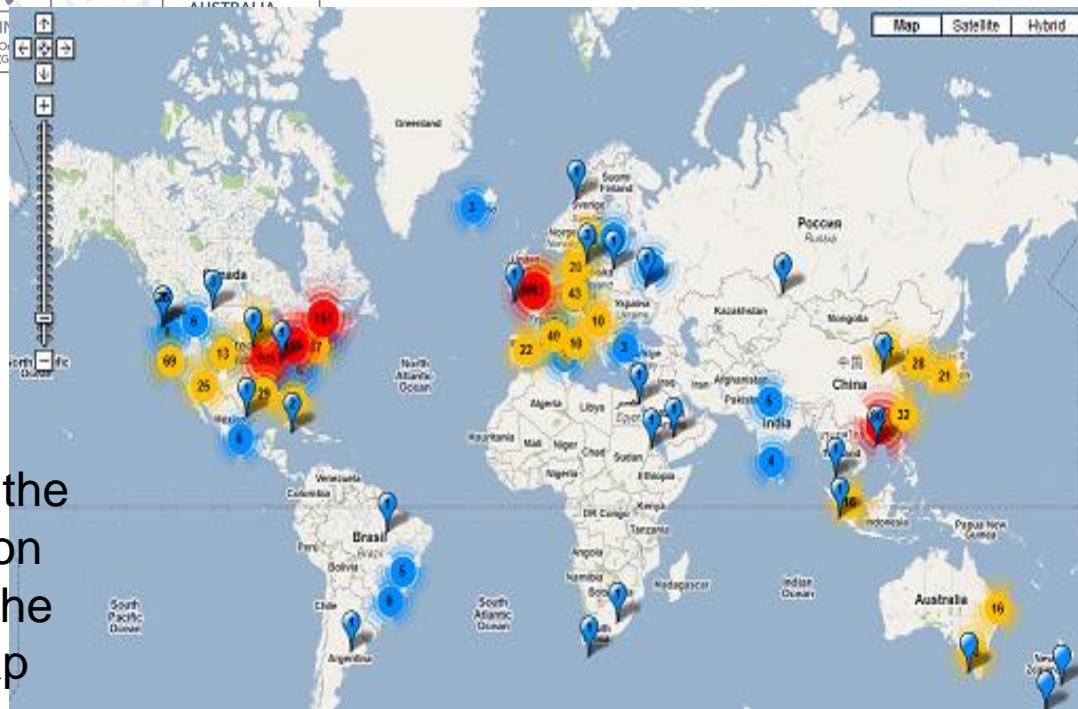
# Each baby to be sequenced at birth: personal reference



# The International Cancer Genome Consortium (ICGC)



BGI genomics map



My dream is to see Russia as one of the countries that are well represented on maps like these, and to take part in the creation of a Russian genomics map

**THANK YOU!**