Iceland – Infrastructure and Potential Participation in Nordic CRC Poject

Workshop on Nordic Big Biomedical Data for Action
Nov 28-30, 2016
Scandic Upplands Väsby

Laufey Tryggvadóttir, Clinical Professor Faculty of Medicine, UI
Managing Director, Icelandic Cancer Registry

- Icelandic Cancer Registry (ICR)
- Family data
- Biological data
- Ethical and legal aspects
- Usage of the data
- Role of the ICR

Icelandic Cancer Registry

- 1954: Established by Icelandic Cancer Society (ICS)

- 2007 **Legislation…**

  …on Directorate of Health and Public Health

  - Cancer registration compulsory
  - Director of Health responsible for the registry
  - A contract - ICS runs the registry

Acta Oncologica, 2012; 51: 880–889

informa
healthcare

99% coverage

ORIGINAL ARTICLE

Data quality at the Icelandic Cancer Registry: Comparability, validity, timeliness and completeness

LARA GUDRUN SIGURDARDOTTIR[1,2], JON GUNNLAUGUR JONASSON[1,3], SIGRUN STEFANSDOTTIR[1], ANNA JONSDOTTIR[1], GUDRIDUR HELGA OLAFSDOTTIR[1], ELINBORG JONA OLAFSDOTTIR[1] & LAUFEY TRYGGVADOTTIR[1,3]

[1]*Icelandic Cancer Registry, Icelandic Cancer Society, Reykjavik, Iceland,* [2]*Centre of Public Health Sciences, University of Iceland, Reykjavik, Iceland, and* [3]*Faculty of Medicine, University of Iceland, Reykjavik, Iceland*

Abstract

Introduction. The nationwide Icelandic Cancer Registry (ICR) was established in 1954 and has been extensively used for research from the outset although formal quality assessment of the registry database has not previously been undertaken. In this paper we report the first formal evaluation of the comparability, validity, timeliness and completeness of the ICR. *Material and methods.* Data from the ICR for the period 1955–2009 (41 994 cancer diagnoses) were used, applying established quantitative and semi-quantitative methods. In order to evaluate the completeness of the ICR, record linkage was performed between the ICR and the population-based Hospital Discharge Registry to identify potential missing cases for tumour diagnoses in 2000 and 2001. *Results.* The registration is in accordance with internationally accepted standards. It has high validity, but random variation in rates is prominent in this small population. Record linkage with the Hospital Discharge Registry revealed that in addition to the 2459 cancers registered in 2000–2001, 21 cases were missing, indicating 99.15% completeness. Tumours of the central nervous system constituted 71%, and haematological malignancies 19% of these missing entries. *Discussion.* The ICR has high completeness, validity and timeliness and is comparable to the cancer registries of the other Nordic Countries. As cancer registries have many important roles, it is of great importance that their data are at all times as complete and valid as possible. Thus the ICR aims to constantly improve and update the data gathering process.

ICR

Overarching aim

To improve public health

Starting in 2017:

Implementation of **Clincal Quality Registration**

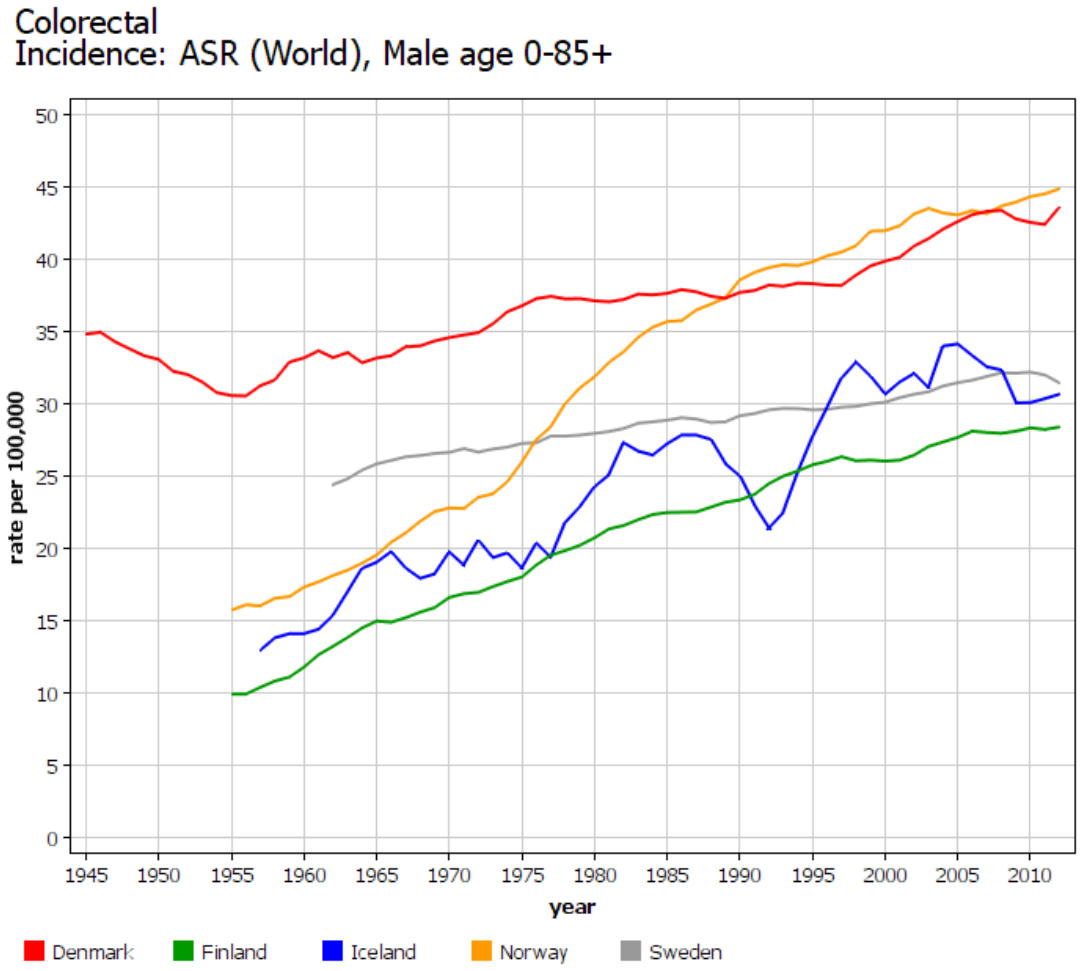
with University Hospital

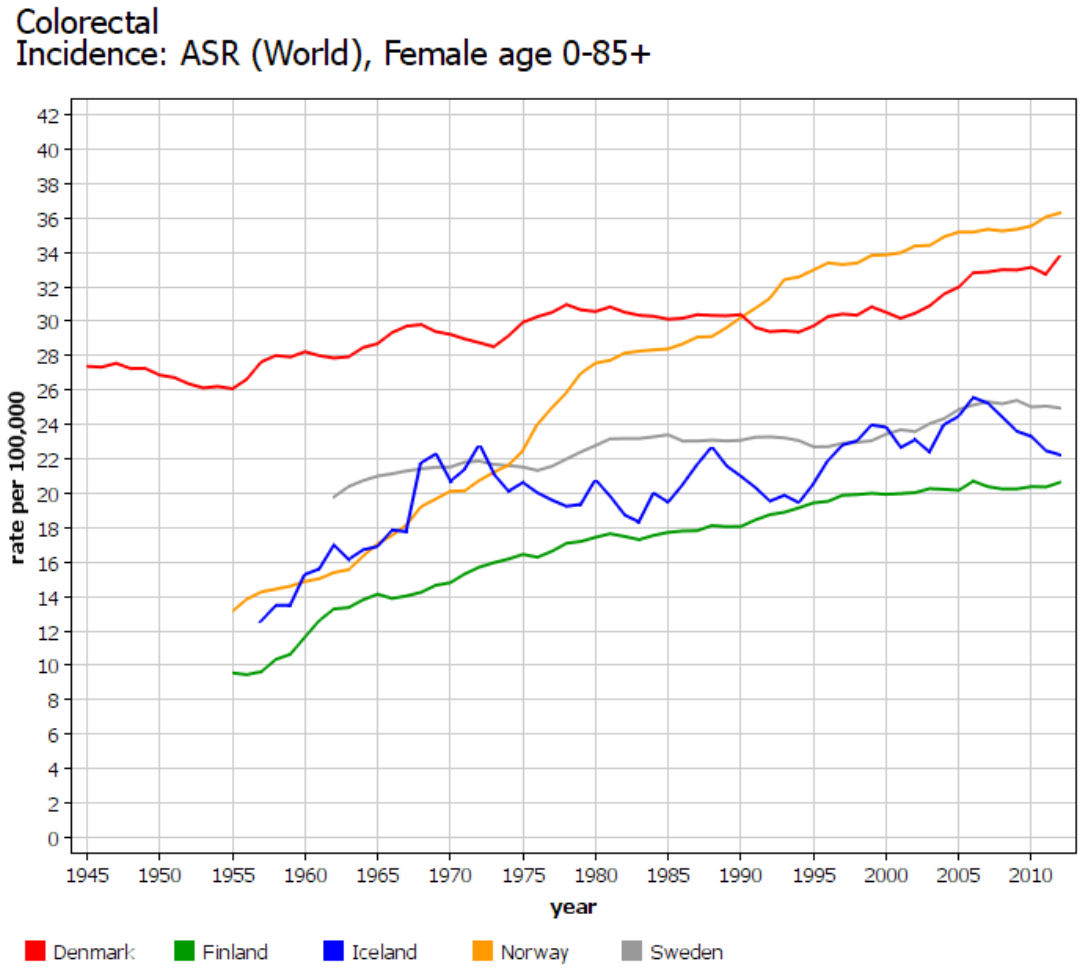
Looking to Swedish INCA system

Since 2010: registration of TNM staging and other histological variables according to INCA form for main cancer types

Colorectal cancer in Iceland

78 males and 64 females diagnosed yearly





NORDCAN © Association of the Nordic Cancer Registries (17.11.2016)

Colorectal Cancer 1955-2015

2528 males & 2320 females -> 4848 individuals

IJC International Journal of Cancer

uicc global cancer control

IJC International Journal of Cancer

Colon cancer in Iceland—a nationwide comparative study on various pathology parameters with respect to right and left tumor location and patients age

Petur Snaebjornsson[1,2,3], Larus Jonasson[2], Thorvaldur Jonsson[1,4], Pall Helgi Möller[1,4], Asgeir Theodors[5] and Jon G. Jonasson[1,2,6]

[1] Faculty of Medicine, University of Iceland, Landspitali, 101 Reykjavik, Iceland
[2] Department of Pathology, Landspitali-University Hospital, Landspitali, 101 Reykjavik, Iceland
[3] Department of Pathology, VU Medical Center, Amsterdam, The Netherlands
[4] Department of Surgery, Landspitali-University Hospital, Landspitali, 101 Reykjavik, Iceland
[5] Department of Gastroenterology, Landspitali-University Hospital, Landspitali, 101 Reykjavik, Iceland
[6] Icelandic Cancer Registry, Icelandic Cancer Society, Reykjavik, Iceland

The Breast Cancer Family Database of the Icelandic Cancer Society

Discovery of *BRCA2* in 1994

Icelandic Cancer Society

University Hospital

Localization of a breast cancer susceptibility gene, BRCA2,
Science; Sep 30, 1994; 265, 5181; ProQuest Central
pg. 2088

variants. Furthermore, probe cyclization reactions depend on an intramolecular reaction as opposed to reaction between pairs of independent probe molecules as in amplification by the polymerase chain reaction. Thus, there should be fewer problems with nonspecific reactions resulting from interactions between noncognate pairs of probe segments with cyclizable probes. The present probe design should permit the simultaneous analysis of multiple gene sequences in a DNA sample.

In conclusion, the nucleic acid probe presented here permits highly specific detection of nucleotide sequences and, although the target is not amplified, highly sensitive detection is possible through efficient reduction of nonspecific signal. Circularizable probes should be applicable in a number of other contexts, including the detection of specific RNA molecules expressed in tissue sections as T4 DNA ligase can assist in ligation reactions involving RNA strands (8). Moreover, immobilized padlock probes could be useful for pre-

Localization of a Breast Cancer Susceptibility Gene, *BRCA2*, to Chromosome 13q12-13

Richard Wooster,* Susan L. Neuhausen,* Jonathan Mangion,* Yvette Quirk,* Deborah Ford,* Nadine Collins, Kim Nguyen, Sheila Seal, Thao Tran, Diane Averill, Patty Fields, Gill Marshall, Steven Narod, Gilbert M. Lenoir, Henry Lynch, Jean Feunteun, Peter Devilee, Cees J. Cornelisse, Fred H. Menko, Peter A. Daly, Wilma Ormiston, Ross McManus, Carole Pye, Cathryn M. Lewis, Lisa A. Cannon-Albright, Julian Peto, Bruce A. J. Ponder, Mark H. Skolnick, Douglas F. Easton,† David E. Goldgar, Michael R. Stratton

A small proportion of breast cancer, in particular those cases arising at a young age, is due to the inheritance of dominant susceptibility genes conferring a high risk of the disease. A genomic linkage search was performed with 15 high-risk breast cancer families that were unlinked to the *BRCA1* locus on chromosome 17q21. This analysis localized a second breast cancer susceptibility locus, *BRCA2*, to a 6-centimorgan interval on chromosome 13q12-13. Preliminary evidence suggests that *BRCA2* confers a high risk of breast cancer but, unlike *BRCA1*, does not confer a substantially elevated risk of ovarian cancer.

THE LANCET

Linkage to *BRCA2* region in hereditary male breast cancer

Steinunn Thorlacius Laufey Tryggvadottir Gudridur H Olafsdottir
Jon Gunnlaugur Jonasson Helga M Ogmundsdottir Hrafn Tulinius Jorunn E Eyfjord

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Vol. 346 No. 8974 Pages 544–545

The complete *BRCA2* gene and mutations in chromosome 13q-linked kindreds

S.V. Tavtigian[1], J. Simard[2], J. Rommens[3], F. Couch[4], D. Shattuck-Eidens[1], S. Neuhausen[5], S. Merajver[6], S. Thorlacius[7], K. Offit[8], D. Stoppa-Lyonnet[9], C. Bélanger[2], R. Bell[1], S. Berry[1], R. Bogden[1], Q. Chen[1], T. Davis[1], M. Dumont[2], C. Frye[1], T. Hattier[1], S. Jammulapati[1], T. Janecki[1], P. Jiang[1], R. Kehrer[1], J.-F. Leblanc[2], J.T. Mitchell[1], J. McArthur-Morrison[3], K. Nguyen[5], Y. Peng[4], C. Samson[2], M. Schroeder[1], S.C. Snyder[1], L. Steele[5], M. Stringfellow[1], C. Stroup[1], B. Swedlund[1], J. Swensen[5], D. Teng[1], A. Thomas[1], T. Tran[1], T. Tran[5], M. Tranchant[2], J. Weaver-Feldhaus[1], A.K.C. Wong[1], H. Shizuya[10], J.E. Eyfjord[7], L. Cannon-Albright[5], F. Labrie[2], M.H. Skolnick[1,5], B. Weber[4], A. Kamb[1] & D.E. Goldgar[5,11]

[1]*Myriad Genetics Inc., Salt Lake City, Utah USA*
[2]*Laboratory of Molecular Endocrinology, CHUL Research Center and Laval University, Quebec City, Canada*
[3]*Department of Genetics, Hospital for Sick Children, University of Toronto, Ontario, Canada*
[4]*Deparment of Hematology-Oncology, University of Pennsylvania, Philadelphia, USA*
[5]*Genetic Epidemiology Group, Department of Medical Informatics and Department of*

trapping, cDNA library screening, genomic sequencing and inter-clone PCR experiments using cDNA as template for amplification ('island hopping'; Fig. 1*a*). The extreme 5' end of the mRNA, including the predicted translational start site, was identified by a modified 5' RACE protocol[7]. The first nucleotide in the sequence (nt 1) is a non-template G, an indication that the mRNA cap is contained in the sequence. A portion of exon 11, which is nearly 5 kilobases (kb) in length, was identified by analysis of roughly 900 kb of genomic sequence in the public domain (ftp://genome.wust1.edu/pub/gscl/brca). This genomic sequence was condensed with our own genomic sequence into a set of 160 sequence contigs. When the condensed sequence was scanned for open reading frames (ORFs), a contiguous stretch of nearly 5 kb was identified which was spanned by long ORFs. This sequence was linked together by island hopping experiments with two previously identified candidate gene fragments (F.C. *et al.*, unpublished)[8]. Our composite *BRCA2* cDNA sequence consists of 11,385 bp but does not include the polyadenylation signal or poly(A) tail.

Conceptual translation of the cDNA reveals an ORF beginning at nt 229 and encoding a protein of 3,418 amino acids. The peptide bears no similarity to other proteins apart from sequence composition. There is no signal sequence at the N terminus and no obvious

Nature Genetics
Vol 13 May 1996

A single *BRCA2* mutation in male and female breast cancer families from Iceland with varied cancer phenotypes

Steinunn Thorlacius, Gudridur Olafsdottir, Laufey Tryggvadottir, Susan Neuhausen, Jon G. Jonasson, Sean V. Tavtigian, Hrafn Tulinius, Helga M. Ögmundsdottir & Jorunn E. Eyfjörd

Am. J. Hum. Genet. 60:1079–1084, 1997

Study of a Single BRCA2 Mutation with High Carrier Frequency in a Small Population

Steinunn Thorlacius,[1] Stefan Sigurdsson,[1] Helga Bjarnadottir,[1] Gudridur Olafsdottir,[2] Jon Gunnlaugur Jonasson,[3], Laufey Tryggvadottir,[2] Hrafn Tulinius,[2,4] and Jorunn E. Eyfjörd[1]

[1]Molecular and Cell Biology Research Laboratory and [2]Cancer Registry, Icelandic Cancer Society, and Departments of [3]Pathology and [4]Preventive Medicine, University of Iceland, Reykjavik

[CANCER RESEARCH 55, 4830–4832, November 1, 1995]

Advances in Brief

Different Tumor Types from BRCA2 Carriers Show Wild-Type Chromosome Deletions on 13q12–q13[1]

Julius Gudmundsson, Gudrun Johannesdottir, Jon Thor Bergthorsson, Adalgeir Arason, Sigurdur Ingvarsson, Valgardur Egilsson, and Rosa Björk Barkardottir[2]

Department of Pathology, Division of Cell Biology, House 14, University Hospital of Iceland, IS-121 Reykjavik, Iceland

Am. J. Hum. Genet. 58:749–756, 1996

Frequent Occurrence of BRCA2 Linkage in Icelandic Breast Cancer Families and Segregation of a Common BRCA2 Haplotype

Julius Gudmundsson,* Gudrun Johannesdottir,* Adalgeir Arason, Jon Thor Bergthorsson, Sigurdur Ingvarsson, Valgardur Egilsson, and Rosa Björk Barkardottir

Department of Pathology, Division of Cell Biology, University Hospital of Iceland, Reykjavik

[CANCER RESEARCH 56, 3663–3665, August 15, 1996]

Advances in Brief

High Prevalence of the 999del5 Mutation in Icelandic Breast and Ovarian Cancer Patients[1]

Gudrun Johannesdottir,[2] Julius Gudmundsson,[2] Jon T. Bergthorsson, Adalgeir Arason, Bjarni A. Agnarsson, Gudny Eiriksdottir, Oskar T. Johannsson, Ake Borg, Sigurdur Ingvarsson, Douglas F. Easton, Valgardur Egilsson, and Rosa Björk Barkardottir[3]

Laboratory of Cell Biology [G. J., J. G., J. T. B., A. A., B. A. A. G. E., S. I., V. E., R. B. B.], Department of Pathology, University Hospital of Iceland, House 14, Landspitalinn, 101 Reykjavik, Iceland; Institute of Oncology, University Hospital, S-221 85 Lund, Sweden; [O. T. J., A. B.]; and CRC Genetic Epidemiology Unit, Department of Community Medicine, Institute of Public Health, University of Cambridge, United Kingdom [D. F. E.]

Nationwide Family Databases

Icelandic Genealogy Database

Complete for all Icelanders born 1810+

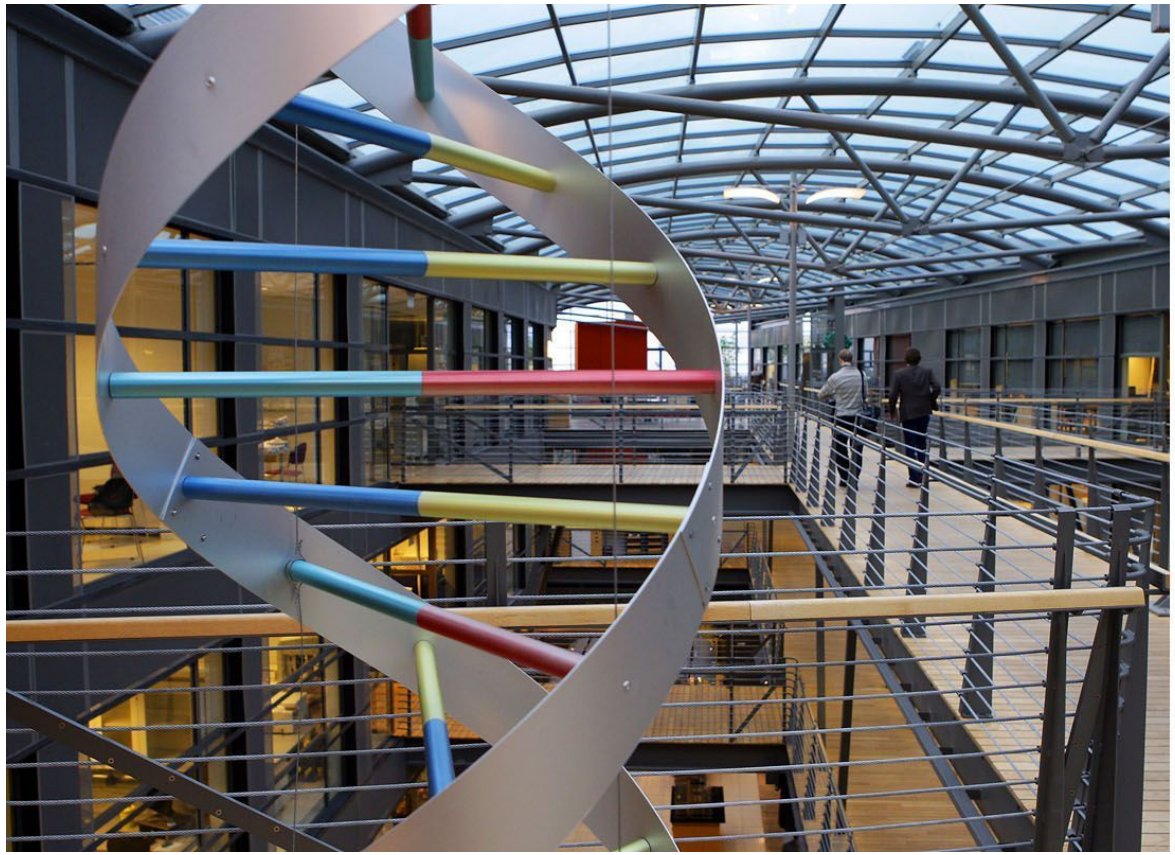
Kept at the University Hospital, accessible to all scientists upon ethical permission

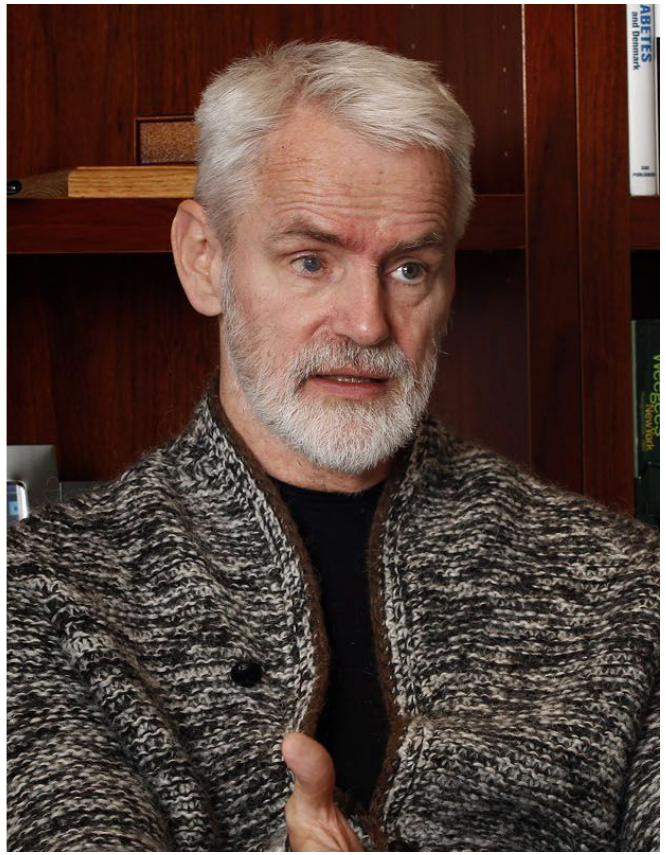
deCODE Family Database – Íslendingabók

Complete for all Icelanders born 1810+

Accessible for researchers affiliated with deCODE company

deCODE company founded in 1996





Biobanks

CRC samples: University Hospital - Department of Pathology

>3000 paraffin embedded CRC samples

>500 fresh frozen CRC samples (starting year 2000)

DNA: deCODE company

deCODE 2015

Genotypes and medical data from 137,000 Icelandic volunteer participants - over 50% of the adult population

Whole genome sequencing of >8,400 of those individuals

-> Imputation of genotypes for 200,000 close relatives – thus family- and genotype information available for 337,000 Icelanders

Possible to search for associations between over 25 million sequence variants and a broad range of phenotypes

Example of work in process

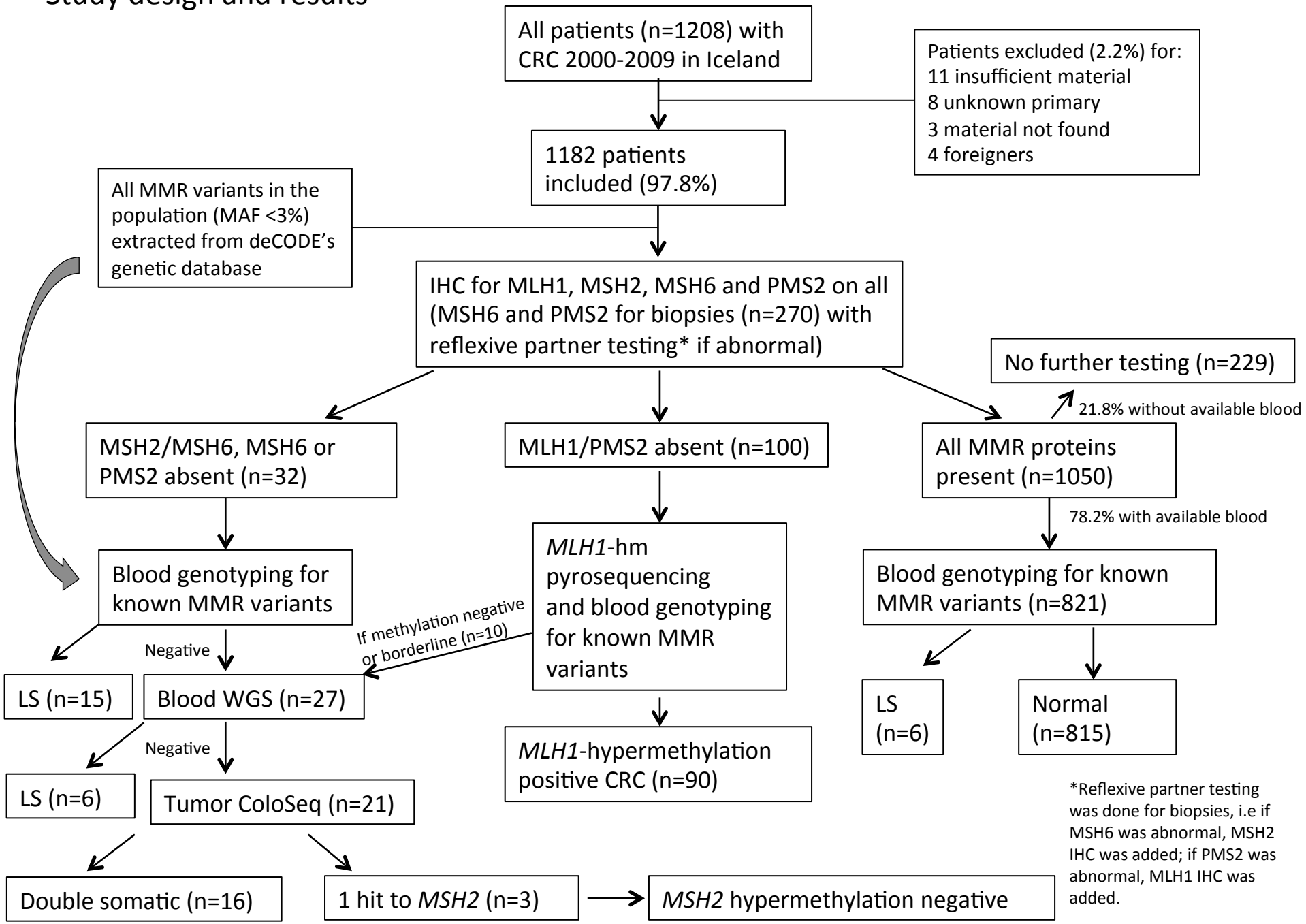
Colorectal cancer and Lynch syndrome

Sigurdis Haraldsdottir MD, MS
Assistant Professor of Medicine
Division of Oncology
Stanford University School of Medicine

PhD thesis will be defended early 2017
Paper accepted by **Nature Communications**

Co-operation with deCODE and University Hospital

Study design and results



Summary

- Highest prevalence of Lynch syndrome so far – 1:226
  - *MSH6* and *PMS2* mutations prevail – 3 founder mutations
  - >1000 individuals carry these in the country
- Translocations can cause Lynch syndrome
- Submit variant data to InSiGHT
  - *MSH6* p.Leu585Pro class 3 variant is pathogenic
  - Other class 3 variants found likely not pathogenic
- Initiate screening program for individuals with Lynch syndrome in Iceland

DNA of all tumour samples being extracted

Planned to do WGS

Nordic co-operation would be very welcomed

Ethical and legal aspects

Permission for individual research projects:

- National Bioethics Committee (& Data Protection Agency)
- UH Pathology Biobank
- Cancer Registry
- Genealogy Database
- University Hospital

Role of the Icelandic Cancer Registry

Co-ordination and initiation of co-operation

2016

FULL PAPER

BJC

British Journal of Cancer (2016), 1–8 | doi: 10.1038/bjc.2016.249

Keywords: *BRCA2* mutation; breast cancer; oestrogen receptor; prognostic factors; treatment; survival

Oestrogen receptor status, treatment and breast cancer prognosis in Icelandic *BRCA2* mutation carriers

Jon G Jonasson[1,2,3], Olafur A Stefansson[4], Oskar T Johannsson[2,5,6], Helgi Sigurdsson[2,5], Bjarni A Agnarsson[2,3], Gudridur H Olafsdottir[1], Kristin K Alexiusdottir[1,5], Hrefna Stefansdottir[1], Rodrigo Munoz Mitev[3], Katrin Olafsdottir[3], Kristrun Olafsdottir[3], Adalgeir Arason[7], Vigdis Stefansdottir[6], Elinborg J Olafsdottir[1], Rosa B Barkardottir[2,7,8], Jorunn E Eyfjord[2,4], Steven A Narod[9] and Laufey Tryggvadóttir*[,1,2]


Thank you