NATIONAL REPORT ON SITUATION/STRATEGIES/SUPPORT INSTITUTIONS AND SPECIALISTS/BEST PRACTICES OF THE GENETIC CONSULTANCY/ ONCOGENETICS IN HUNGARY

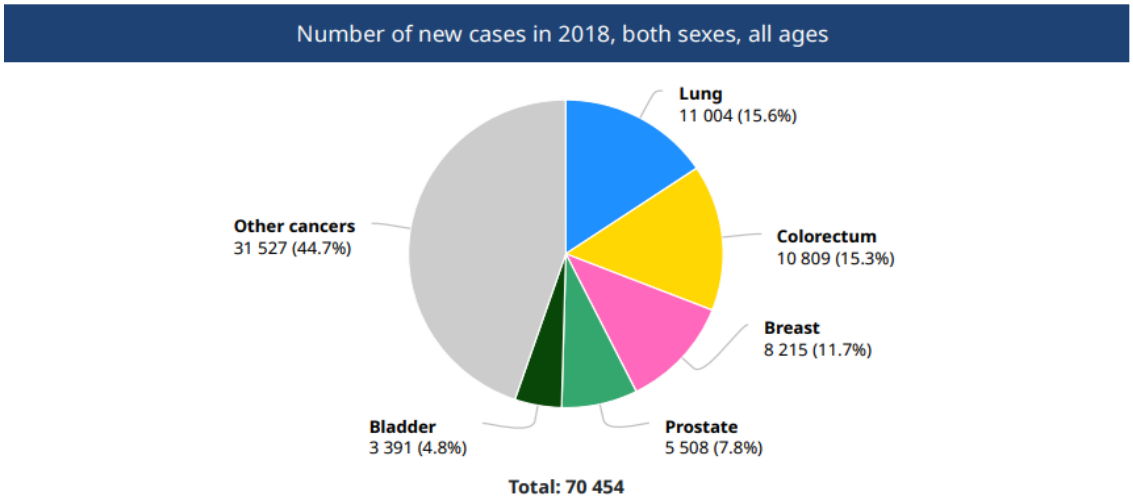
Report created in the framework of the project Promoters of advanced oncogenetics open online training and multimedia raise awareness on multidisciplinary assessment of patients and their families at risk of hereditary or familial cancer, Reference number 2018-1-RO01-KA202-049189, Strategic Partnerships for vocational education and training Erasmus+ programme

1. The current epidemiological situation on cancers, in general, and on hereditary cancers (breast, ovarian, colorectal cancer and other) in Hungary

a. Source: http://gco.iarc.fr/today/home

CANCER TODAY enables a comprehensive assessment of the cancer burden worldwide in 2018, based on the GLOBOCAN estimates of incidence, mortality and prevalence for year 2018 in 185 countries or territories for 36 cancer types by sex and age group.

Hungary



Source: The Global Cancer Observatory

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Summary statistic 2018			
	Males	**Females**	**Both sexes**
Population	4 610 879	5 077 967	9 688 846
Number of new cancer cases	35 281	35 173	70 454
Age-standardized incidence rate (World)	427.1	330.6	368.1
Risk of developing cancer before the age of 75 years (%)	63.4	49.2	54.9
Number of cancer deaths	17 586	15 424	33 010
Age-standardized mortality rate (World)	203.2	122.0	155.8
Risk of dying from cancer before the age of 75 years (%)	42.9	27.7	33.6
5-year prevalent cases	85 345	99 932	185 277
Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases)	Lung Colorectum Prostate Bladder Kidney	Breast Colorectum Lung Corpus uteri Cervix uteri	Lung Colorectum Breast Prostate Bladder

Source: The Global Cancer Observatory

Estimated number of new cases in 2018, Hungary, females, all ages

* Crude and age-standardized rates per 100 000

ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C00-97	**All cancers**	35 173	[34435.1-35926.7]	692.7	330.6	-
C50	Breast	8 215	[7518.2-8976.4]	161.8	85.5	-
C18-21	Colorectum	4 694	Not available	92.4	36.8	-
C33-34	Lung	4 537	[4278.6-4811.0]	89.3	41.4	-
C54	Corpus uteri	1 919	[1625.9-2264.9]	37.8	18.2	-
C53	Cervix uteri	1 312	[1124.5-1530.8]	25.8	17.2	-
C56	Ovary	1 305	[1153.0-1477.0]	25.7	13.2	-
C25	Pancreas	1 233	[1116.8-1361.3]	24.3	9.1	-
C67	Bladder	1 057	[873.7-1278.8]	20.8	9.1	-
C73	Thyroid	999	[731.4-1364.6]	19.7	13.6	-
C64-65	Kidney	991	[819.8-1197.9]	19.5	8.8	-
C43	Melanoma of skin	944	[739.1-1205.7]	18.6	10.1	-
C16	Stomach	861	[751.2-986.9]	17.0	6.3	-
C82-86, C96	Non-Hodgkin lymphoma	809	[634.3-1031.9]	15.9	7.4	-
C91-95	Leukaemia	686	[573.3-820.8]	13.5	7.2	-
C23-24	Gallbladder	477	[405.8-560.6]	9.4	3.2	-
C00-06	Lip, oral cavity	417	[295.7-588.0]	8.2	3.8	-
C70-72	Brain, nervous system	406	[323.7-509.2]	8.0	4.7	-
C22	Liver	317	[248.3-404.8]	6.2	2.4	-
C51	Vulva	251	[177.4-355.1]	4.9	2.0	-
C88+C90	Multiple myeloma	219	[163.3-293.7]	4.3	1.8	-
C09-10	Oropharynx	216	[160.5-290.7]	4.3	2.4	-

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ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C32	Larynx	177	[117.8-266.0]	3.5	2.0	-
C15	Oesophagus	118	[79.2-175.8]	2.3	1.1	-
C81	Hodgkin lymphoma	93	[48.9-177.0]	1.8	1.9	-
C07-08	Salivary glands	87	[51.6-146.6]	1.7	1.00	-
C52	Vagina	68	[43.3-106.7]	1.3	0.55	-
C12-13	Hypopharynx	55	[37.0-81.8]	1.1	0.58	-
C11	Nasopharynx	39	[22.0-69.2]	0.77	0.47	-
C45	Mesothelioma	19	[10.1-35.7]	0.37	0.17	-
C46	Kaposi sarcoma	3	[1.4-6.4]	0.06	0.01	-

Estimated number of new cases in 2018, Hungary, males, all ages

* Crude and age-standardized rates per 100 000

ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C00-97	**All cancers**	35 281	[34594.4-35981.2]	765.2	427.1	-
C33-34	Lung	6 467	[6158.1-6791.4]	140.3	77.4	-
C18-21	Colorectum	6 115	Not available	132.6	70.6	-
C61	Prostate	5 508	[5021.9-6041.1]	119.5	60.2	-
C67	Bladder	2 334	[1990.3-2737.0]	50.6	26.9	-
C64-65	Kidney	1 305	[1096.3-1553.4]	28.3	16.6	-
C16	Stomach	1 228	[1072.9-1405.5]	26.6	13.8	-
C25	Pancreas	1 093	[956.7-1248.7]	23.7	12.9	-
C32	Larynx	922	[788.0-1078.7]	20.0	12.0	-
C00-06	Lip, oral cavity	893	[739.8-1077.9]	19.4	11.8	-
C43	Melanoma of skin	780	[576.6-1055.2]	16.9	10.3	-
C82-86, C96	Non-Hodgkin lymphoma	774	[642.5-932.4]	16.8	10.4	-
C22	Liver	770	[665.5-890.9]	16.7	9.2	-
C91-95	Leukaemia	765	[648.5-902.4]	16.6	10.6	-
C15	Oesophagus	628	[509.8-773.6]	13.6	8.1	-
C62	Testis	554	[377.8-812.5]	12.0	10.7	-
C09-10	Oropharynx	518	[410.3-654.0]	11.2	7.3	-
C12-13	Hypopharynx	471	[391.8-566.3]	10.2	6.5	-
C70-72	Brain, nervous system	434	[354.0-532.1]	9.4	6.6	-
C23-24	Gallbladder	279	[222.3-350.1]	6.1	3.0	-
C88+C90	Multiple myeloma	230	[172.5-306.6]	5.0	2.7	-
C73	Thyroid	192	[120.9-305.0]	4.2	3.0	-
C81	Hodgkin lymphoma	128	[75.1-218.2]	2.8	2.7	-

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ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C60	Penis	113	[72.5-176.0]	2.5	1.3	-
C07-08	Salivary glands	78	[51.4-118.3]	1.7	0.98	-
C11	Nasopharynx	69	[47.2-100.9]	1.5	0.98	-
C45	Mesothelioma	28	[17.0-46.1]	0.61	0.36	-
C46	Kaposi sarcoma	7	[2.7-18.3]	0.15	0.06	-

Estimated number of deaths in 2018, Hungary, females, all ages

* Crude and age-standardized rates per 100 000

ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C00-97	**All cancers**	15 424	[15126.6-15727.3]	303.7	122.0	-
C33-34	Lung	3 535	[3367.8-3710.5]	69.6	30.9	-
C50	Breast	2 212	[2055.7-2380.1]	43.6	17.9	-
C18-21	Colorectum	2 209	Not available	43.5	14.8	-
C25	Pancreas	1 109	[1021.9-1203.5]	21.8	7.9	-
C56	Ovary	777	[701.4-860.7]	15.3	6.6	-
C16	Stomach	628	[561.0-703.0]	12.4	4.3	-
C53	Cervix uteri	499	[438.7-567.6]	9.8	5.1	-
C91-95	Leukaemia	434	[374.2-503.4]	8.5	3.4	-
C54	Corpus uteri	413	[359.6-474.3]	8.1	2.9	-
C23-24	Gallbladder	392	[343.0-448.0]	7.7	2.5	-
C64-65	Kidney	373	[318.9-436.3]	7.3	2.6	-
C70-72	Brain, nervous system	342	[283.6-412.4]	6.7	3.4	-
C67	Bladder	301	[257.1-352.3]	5.9	2.0	-
C22	Liver	292	[238.6-357.4]	5.8	2.1	-
C82-86, C96	Non-Hodgkin lymphoma	286	[233.9-349.7]	5.6	2.1	-
C43	Melanoma of skin	182	[148.7-222.8]	3.6	1.5	-
C00-06	Lip, oral cavity	145	[109.1-192.6]	2.9	1.3	-
C88+C90	Multiple myeloma	142	[111.4-181.0]	2.8	1.0	-
C51	Vulva	106	[79.6-141.2]	2.1	0.66	-
C15	Oesophagus	99	[71.2-137.7]	1.9	0.88	-
C09-10	Oropharynx	73	[57.1-93.3]	1.4	0.76	-
C32	Larynx	70	[50.0-98.0]	1.4	0.75	-
C73	Thyroid	65	[50.2-84.1]	1.3	0.42	-
C12-13	Hypopharynx	39	[28.1-54.1]	0.77	0.39	-
C52	Vagina	32	[22.1-46.4]	0.63	0.22	-
C07-08	Salivary glands	23	[14.9-35.4]	0.45	0.19	-
C11	Nasopharynx	19	[11.8-30.5]	0.37	0.22	-
C45	Mesothelioma	16	[9.5-26.9]	0.32	0.14	-

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ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C81	Hodgkin lymphoma	16	[9.4-27.2]	0.32	0.19	-
C46	Kaposi sarcoma	1	[0.50-1.9]	0.02	0.00	-

Estimated number of deaths in 2018, Hungary, males, all ages

* Crude and age-standardized rates per 100 000

ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C00-97	**All cancers**	17 586	[17271.4-17906.3]	381.4	203.2	-
C33-34	Lung	5 358	[5145.6-5579.2]	116.2	62.9	-
C18-21	Colorectum	2 867	Not available	62.2	31.2	-
C61	Prostate	1 225	[1134.9-1322.2]	26.6	11.8	-
C25	Pancreas	969	[868.0-1081.8]	21.0	11.2	-
C16	Stomach	895	[800.5-1000.7]	19.4	9.9	-
C67	Bladder	649	[568.9-740.3]	14.1	6.8	-
C22	Liver	628	[556.7-708.5]	13.6	7.3	-
C15	Oesophagus	493	[414.9-585.8]	10.7	6.3	-
C00-06	Lip, oral cavity	461	[394.6-538.6]	10.0	6.1	-
C64-65	Kidney	458	[396.6-529.0]	9.9	5.3	-
C32	Larynx	456	[400.5-519.2]	9.9	5.7	-
C91-95	Leukaemia	438	[382.1-502.1]	9.5	5.2	-
C70-72	Brain, nervous system	354	[299.1-418.9]	7.7	4.8	-
C12-13	Hypopharynx	320	[274.8-372.6]	6.9	4.3	-
C82-86, C96	Non-Hodgkin lymphoma	299	[256.3-348.8]	6.5	3.5	-
C09-10	Oropharynx	267	[220.2-323.7]	5.8	3.7	-
C23-24	Gallbladder	216	[179.0-260.6]	4.7	2.3	-
C43	Melanoma of skin	169	[131.6-217.0]	3.7	2.0	-
C88+C90	Multiple myeloma	138	[108.8-175.0]	3.0	1.5	-
C62	Testis	42	[30.6-57.6]	0.91	0.70	-
C11	Nasopharynx	42	[30.7-57.5]	0.91	0.54	-
C07-08	Salivary glands	37	[26.2-52.2]	0.80	0.45	-
C60	Penis	31	[21.5-44.7]	0.67	0.34	-
C73	Thyroid	30	[20.5-44.0]	0.65	0.32	-
C45	Mesothelioma	25	[16.6-37.7]	0.54	0.31	-
C81	Hodgkin lymphoma	22	[14.2-34.2]	0.48	0.33	-
C46	Kaposi sarcoma	2	[0.90-4.4]	0.04	0.02	-

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Estimated number of prevalent cases in 2018, Hungary, males, all ages

*** Proportions per 100 000

ICD	Cancer	5-year	Proportions***
C00-97	**All cancers**	85 345	1850.9
C61	Prostate	18 340	397.8
C18-21	Colorectum	16 143	350.1
C67	Bladder	7 261	157.5
C33-34	Lung	6 455	140.0
C64-65	Kidney	3 300	71.6
C32	Larynx	2 826	61.3
C00-06	Lip, oral cavity	2 641	57.3
C43	Melanoma of skin	2 501	54.2
C62	Testis	2 392	51.9
C82-86, C96	Non-Hodgkin lymphoma	2 217	48.1
C91-95	Leukaemia	2 082	45.2
C16	Stomach	1 739	37.7
C09-10	Oropharynx	1 697	36.8
C70-72	Brain, nervous system	1 123	24.4
C12-13	Hypopharynx	796	17.3
C25	Pancreas	669	14.5
C73	Thyroid	669	14.5
C15	Oesophagus	668	14.5
C88+C90	Multiple myeloma	563	12.2
C22	Liver	536	11.6
C81	Hodgkin lymphoma	517	11.2
C60	Penis	358	7.8
C23-24	Gallbladder	304	6.6
C11	Nasopharynx	214	4.6
C07-08	Salivary glands	200	4.3
C45	Mesothelioma	31	0.67
C46	Kaposi sarcoma	18	0.39

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Estimated number of prevalent cases in 2018, Hungary, females, all ages

*** Proportions per 100 000

ICD	Cancer	5-year	Proportions***
C00-97	**All cancers**	99 932	1968.0
C50	Breast	31 217	614.8
C18-21	Colorectum	13 064	257.3
C54	Corpus uteri	6 874	135.4
C33-34	Lung	5 268	103.7
C53	Cervix uteri	4 096	80.7
C73	Thyroid	3 808	75.0
C56	Ovary	3 547	69.9
C67	Bladder	3 094	60.9
C43	Melanoma of skin	3 060	60.3
C64-65	Kidney	2 607	51.3
C82-86, C96	Non-Hodgkin lymphoma	2 321	45.7
C91-95	Leukaemia	1 809	35.6
C16	Stomach	1 275	25.1
C00-06	Lip, oral cavity	1 250	24.6
C70-72	Brain, nervous system	1 188	23.4
C51	Vulva	779	15.3
C09-10	Oropharynx	771	15.2
C25	Pancreas	734	14.5
C32	Larynx	552	10.9
C88+C90	Multiple myeloma	547	10.8
C23-24	Gallbladder	425	8.4
C81	Hodgkin lymphoma	383	7.5
C07-08	Salivary glands	235	4.6
C22	Liver	212	4.2
C52	Vagina	189	3.7
C11	Nasopharynx	132	2.6
C15	Oesophagus	131	2.6
C12-13	Hypopharynx	110	2.2
C45	Mesothelioma	24	0.47
C46	Kaposi sarcoma	8	0.16

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2. The current situation on the National Strategies about the models used in genetic risk assessment and genetic tests for hereditary cancers in Hungary

The tertiary care of cancer patients in Hungary is mainly performed in five large patient care units:

1. Semmelweis University, Budapest, Hungary
2. National Oncology Institute, Budapest, Hungary
3. University of Debrecen, Hungary
4. University of Pécs, Hungary
5. University of Szeged, Hungary

The Budapest based Semmelweis University and Molecular Genetics Department of National Oncology Institute carry out their hereditary cancer patient care and related genetic counselling in a coordinated manner.

Although there is a National Oncogenetic Healthcare in Budapest Hungary but decentralization of this unit is still missing, subsequently we would like to develop new Oncogenetic Healthcare Institutions at the tree non-capital Universities too. Consequently there is further need for National Strategies for Diagnosis and Oncogenetic management of hereditary cancer patients. Diagnosis of hereditary risk for breast / ovarian cancer through BRCA genes and for familiar adenomatous polyposis through APC gene has already been performed in the non-capital Hungarian Universities at risk patients mainly in a context of scientific research, although the oncogenetic counselling is inevitable in these cases. We have clinical genetic counselling without oncogenetic specifity. The screening of hereditary gene predisposition genes is currently a standardized practice in Western European countries, which allows personalised monitoring and genetic counselling for those at risk in these families.

We would like to improve the Hungarian Oncogenetic Healthcare in a following way: The necessity to decentralize the oncogenetic patient care in Hungary according to the increasing clinical need, to implement and develop Medical Oncogenetic Institutes and train oncogeneticists for genetic consultations. The long-term goal is to generate an oncogenetic expertise that will connect Hungary to similar European structures designed to monitor patients with hereditary cancer risk.

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The need to identify and recruit patients with hereditary risk for monitoring: Hereditary Ovary Cancer (HBOC), Hereditary Colorectal Cancer (HNPCC), Familiar Adenomatous Polyposis (FAP). Patient identification will generate a consistent databases and a representative biobanks, according to the European normal and models, including clinical, epidemiological, morphopathological, moleculargenetic family history data. The information will contribute to complete the National Cancer Registry in Hungary.

The need for molecular testing of genetic risk factors (BRCA1, BRCA2, MMR, APC etc). The molecular genetic studies will need to include a pre-screening - dedicated and rapid techniques - of known, specific, recurrent or frequent mutations in the population and in particular, a full screening of mutations by complete gene or genome sequencing.

The need to interpret the results obtained, which will be at the basis of an epidemiological assessment of the risk factors for cancer in the Hungarian population. There are also no national approved risk assessment models available in Hungary.

3. The current practical situation on Genetic Testing Availability for HBOC and CCR in Hungary

Genetic tests and genetic counselling for hereditary cancers are available in Hungary however it is centralized in our capital Budapest. Universities of Debrecen, Pécs and Szeged need to estabilish and keep continuously maintaining a high-throughput diagnostic tool parks and oncogenetic councelling.

To reach our purpose there is a need for well-defined national funding system taking into account the increasing clinical needs and a good training program for an Oncological license exam with oncogenetic specifities or Clinical Genetic Board exam with special oncogenetic training.

Overview of diagnosis and care of cancer patients at the University of Debrecen

University of Debrecen is a high-level tertiary healtcare provider, one of the four universities in Hungary with medical education profile. Therefore, it provides comprehensive diagnostic and therapeutic approaches in all disciplines. The University has obligatory care

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provider responsibility for three Counties, namely Hajdú-Bihar, Szabolcs-Szatmár-Bereg and Szolnok.

Diagnostic possibilities

Genetic testing of *BRCA1/2* genes in the Department of Laboratory Medicine at the University of Debrecen include targeted analysis of the most common mutations by Sanger sequencing. The number of genetic tests performed in the **last 5-year period (2013-2018) was 690**. Most of the samples (77%) are referred from Department of Oncology, Radiotherapy and Surgery. The remaining 23% of samples are received from Department of Obstetrics and Gynecology. The genetic service is provided for patients from north-east part of Hungary, mainly from three counties (Hajdú-Bihar, Szabolcs-Szatmár-Bereg, Borsod-Abaúj-Zemplén) but our laboratory receive high number of samples from Bács-Kiskun county, too. Clinical genetic service is limited, clinical geneticists are working in the Department of Obstetrics and Gynecology and Department of Pediatrics. These professionals are avaliable when requested.

Other biomarkers

Analysis of human epididymis protein 4 (HE4) levels for monitoring the clinical status of patients with ovarian cancer

Ovarian cancer represents one of the most common malignancies in women worldwide. In the last 20 years, the survival ratio of patients with this tumor type has been significantly improved, as subjects can be treated by current surgery and chemotherapy (first-line paclitaxel-carboplatin combined medication) resulting in about 80% survival ratio. Notably, in 75% of treated subjects relapse develops within the first 3 years after treatment (5).

For more than two decades, CA-125 was the only tumor maker for laboratory monitoring of ovarian cancer patients (6). In 2003, a new biomarker human epididymis protein 4 (HE4) was described to be overexpressed by ovarian cancer cells, which is a 25 kDa molecular weight protein (7). Since then, the analysis of HE4 levels has been thoroughly investigated in several clinical studies to be compared with the characteristics of “gold standard” CA-125 (8). Although CA-125 shows a relatively high sensitivity (80%) in advanced stages, but is less sensitive (only 40%) in early stages of ovarian tumors. Moreover, a number of non-malignant gynecological diseases, such as ovarian cyst, endometriosis and pelvic inflammation may elevate its serum level without ovarian malignancy. In contrast, HE4

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demonstrates higher sensitivity (91%) with 94% specificity, and its concentration is rarely increased by benign conditions. When both tumor markers are analyzed in the same sample, their diagnostic characteristics can be further improved (8). Apart from the detection of ovarian cancer, the main indication of the measurement of these tumor markers is the evaluation of prognosis and follow-up after treatment. It was described that the positive predictive value in relation to platinum resistance was higher for the combination of these markers than for the markers individually (9). Importantly, HE4 levels need to be evaluated in relation to renal function, as HE4 can be falsely increased by impaired kidney function (10). Overall, HE4 has been proposed as the most promising biomarker that may complement the CA125 expression and has been approved by the FDA in monitoring the follow-up and relapse of OC patients (11).

The investigation of HE4 is available at our Department from December 2010, and annually over 4000-4500 analyses are performed. To demonstrate the efficacy of HE4 and CA-125 in the follow-up of ovarian tumors, some typical cases are presented below via the alteration of these biomarkers (Figure 1):

- In Patient “A” the level of HE4 normalized at much earlier time point after successful surgery and chemotherapy than that of CA-125.
- Although Patient “B” did not have ovarian cancer after effective treatment, CA-125 remained abnormal (over 35 kIU/L) compared to HE4 (less than 140 pmol/L).
- In Patient “C” HE4 together with CA-125 indicated the development of relapse of ovarian cancer despite of Caelyx (doxorubicin) treatment.

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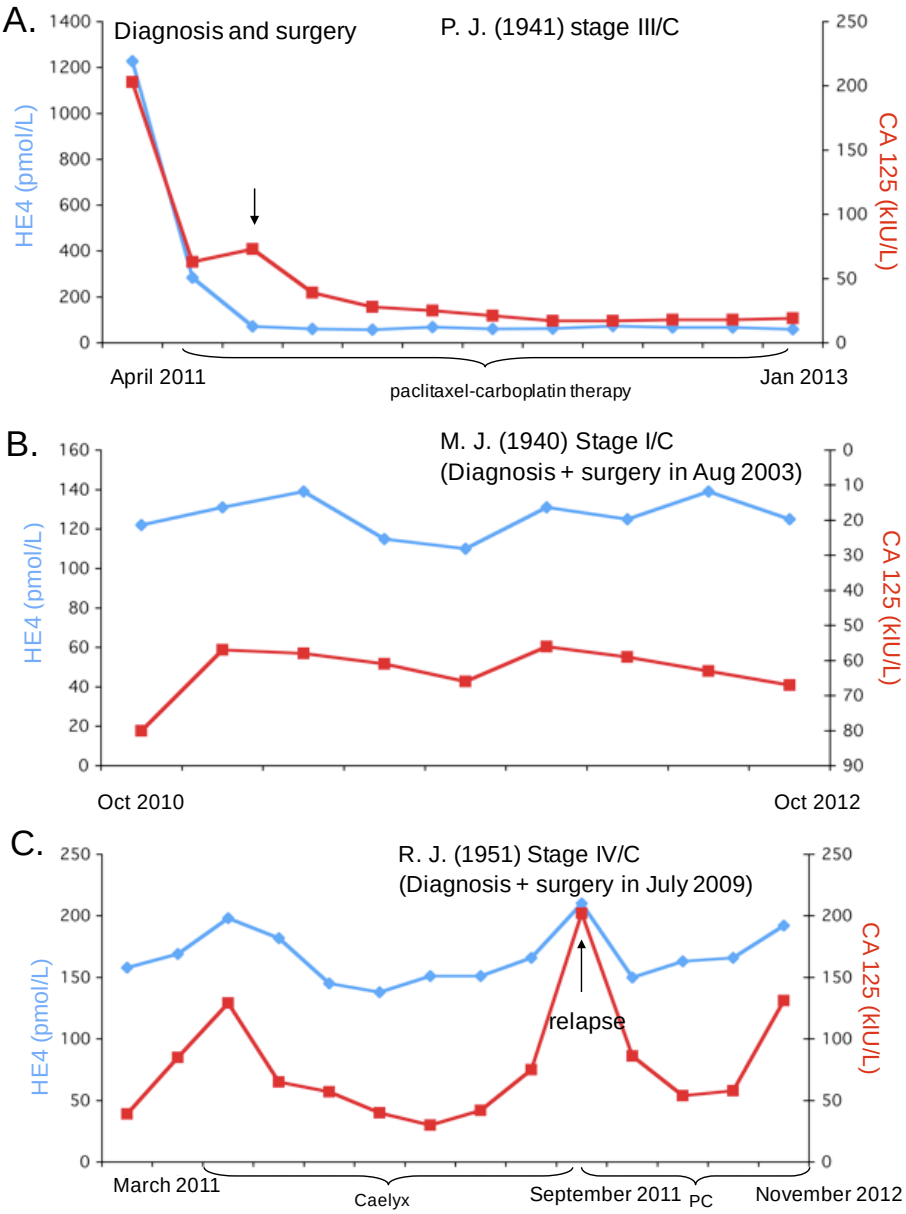

Figure 1. The follow-up of three ovarian cancer patients among different clinical conditions via the regular analysis of serum HE4 and CA-125. These cases show that HE4 is more reliable than CA-125 not only for the detection of ovarian cancer, but also for its follow-up.

Other diagnostic possibilities

As it was mentioned University of Debrecen is a high-level tertiary healthcare provider, meaning that all state-of-the art diagnostic possibilities exist in the Clinical Center. In addition to the pathology service, Department of Radiology provides X-ray, ultrasound, CT, MR, PET-CT, scintigraphy services for both primer tumor and metastasis analyses.

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Therapeutic interventions

Used guidelines

1. NCCN Clinical Practice Guidelines in Oncology (3)
http://www.nccn.org/professionals/physician gls/default nojava.aspx
2. Clinical studies
3. ESMO
4. St. Gallen Consensus5. Szakirodalom: Magyar Onkológia, Journal of Clinical Oncology
5. Guidelines by the National Institute of Pharmacy and Nutrition
6. Protocol by the Ministry Human Capacities about the care of breast cancers
7. Protocol by the Ministry Human Capacities about the care of colorectal cancers

Overview of diagnosis and care of cancer patients at the University of Pécs

The Department of Medical Genetics in Pécs, Hungary is a regional diagnostic, educational and research collaboration center to provide effective preventive and therapeutic genomic medicine in healthcare. Our main aims are the early assessment and diagnosis of birth defects and genetic diseases, strategy provision for effective prevention of genetic disorders.

Our diagnostic services encompass the in-house analysis of domestic and international samples on the cytogenetic and molecular level. **The *BRCA1* and *BRCA2* tumor suppressor genes have been analyzed in around 50 cases** while gene tests for **RET proto oncogene have been run around 10 cases**. One of our most commonly requested molecular tests is **Neurofibromatosis 1 gene** sequencing which have been conducted in **720 cases**; ***TSC1*** and ***TSC2*** have been examined in **150** patients.

Currently, we are in the process of optimizing the diagnostic workflow on both of our Next-Generation Sequencing instruments. (Human hereditary cancer panel: *BRCA1,BRCA2, PALB2, CHEK2, BARD1, BRIP1, RAD51C, RAD51D, TP53, MRE11A, RAD50, NBN, FAM175A, ATM, STK11, MEN1, PTEN, CDH1, MUTYH, BLM, XRCC2, MLH1, MSH6, PMS2, MSH2, 3' UTR of EPCAM).*

Our Genetic Counselling services have been specialized in the phenotypic diagnosis of rare congenital anomaly and genetic disease in the family, but we have also been focusing on the complications and probable treatment options of rare cancers, too. Oncologic patients are referred to either of our two specialist outpatient clinics, one of which is run as a collaboration with the Department of Oncotherapy of the University of Pécs. The Department of

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Oncotherapy cares for approximately 300-400 outpatients while providing around 150 radiation therapy treatments and administering 60-80 infusions on a daily basis, covering almost two counties in the Southwest of Hungary. Our Genetic Counselling Clinic sees patients who have been referred by their oncologists, surgeons from the Department of Oncotherapy due to their rare or hereditary cancers. Our team, in turn, collects and completes the information about the cancer cases of the individual's family, assesses the degree of risk for the disease, and eventually, conducts the appropriate gene tests. We also discuss the significance of the test, especially regarding timely screening programs, early identification and prevention for those who are still symptom-free, but nevertheless carrying the predisposing genes within the family.

Our Pediatric Oncologic Counselling is somewhat different in terms of focusing on the detection and investigation of known, early-onset cancer-syndromes. This clinic sees patients from across Hungary.

The Department of Medical Genetics conducts a successful biobanking project housing over 10 000 DNA samples covering a wide spectrum of rare diseases.

Our Institute participates in two oncology ERNs, namely in JARC, which deals with rare cancers and in GENTURIS for genetic tumor risk syndromes.

The Department offers graduate and postgraduate programs, engaging researchers and collaborators across Hungary and internationally.

Overview of diagnosis and care of cancer patients at the University of Szeged

The Department of Medical Genetics in Szeged, Hungary is a regional diagnostic, educational and research Center of Bács-Kiskun, Csongrád, Békés counties to provide efficient genetic medicine in healthcare.

We have started to establish the diagnostic workflow and genetic counselling of the hereditary tumor syndromes in our Institute.

Beside HBOS, we have been investigating the genetic backround of patients suffering from familiar adenomatous polyposis (FAP) since one year. Genetic screening in families with high risk to develop colorectal cancer (CRC) prevents incurable disease and permits personalized therapeutic and follow-up strategies. The advancement of next-generation sequencing (NGS) technologies has revolutionized the throughput of DNA sequencing. A series of probands for familial adenomatous polyposis **(FAP; 8 cases)** have been investigated

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for intragenic mutations of CRC familial syndromes-associated genes (*APC, MUTYH, MLH1, MSH2, MSH6, PMS2, SMAD4, STK11, PTEN*) applying Illumina Next Seq 500 NGS panel and conventional Sanger sequencing. We have found a c.3927_3931delAAAGA (ID: rs 121913224) pathogen variant in one case. Our future plan is to extend these investigations to whole exom sequencing.

We have collected current data concerning to several frequently occurring types of cancers from the Patient Register of Albert Szentgyörgyi Clinical Center of Szeged University. Data shows slight increase during the last four years (between 2105-2018) in case of colon cancer however the number of breast and ovarian cancers are being slowly decreased.
516 cases of colon cancer, 1393 cases of breast cancer and 151 cases of ovarian cancer patients were represented at the Albert Szentgyörgyi Clinical Center of Szeged University in 2018.

Out of total number of cases, 315 of colon cancer, 592 of breast cancer and 67 of ovarian cancer patients underwent surgery. Chemo and Radiotherapy were applied in case of 313 of colon cancer, 1163 breast cancer and 111 ovarian cancer patient.

The Department of Medical Genetics is involed in the molecular and cytogenetic diagnostic work focusing on onkohematology tumor disorders, rare genetic diseases, prenatal dignostic care of fetuses and postnatal diagnostic care of genetically affected patients, as well as the genetic councelling. Graduate and postgraduate education programs and research work across Hungary and internationally are also main tasks of the Institute.

Diagnosis and care of cancer patients of Molecular Genetics Department of National Oncology Institute, Budapest, Hungary

Detection of the inherited mutation of *BRCA* genes

BRCA mutations inherited at any point of the gene may occur. About 3800 *BRCA1* and *BRCA2* variants are known, but some of them are not pathogenic (Breast Cancer Information Core). Most pathogenic mutations introduce premature termination codons through small frameshift deletions or insertions, nonsense or splice junction alterations, missense mutations within specific residues of functional motifs or large deletions or duplications.

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Small sequence alterations can be detected by traditional sequencing methods as well as New Generation Sequencing while the large genomic rearrangements are analysed by MLPA. **At the Department of Molecular Genetics of National Oncology Institute** nearly 500 *BRCA 1* and *BRCA 2* pathogenic mutations have been identified since 1995 and more than twice variants of unknown significance (VUS), furthermore thousands of harmless polymorphisms out of **9000** genetic tests have been detected.

Forty different types *BRCA1* and *BRCA2* mutation and 78 types of uncertain significance variants were submitted from Hungary to the central database of CIMBA (Consortium of Investigators of Modifiers of BRCA 1 and *BRCA*2).

Most common *BRCA1* mutations in Hungary:

c.5266dup; c.181T > G; c.68_69del; c.5278-?_5406+?del; c.5251C > T
185delAG, 5382insC, T300G >80% (4,12)

Frequently observed *BRCA*2 mutations in Hungary:

c.9097dup; c.5946del; c. 7913_7917del; c.6656C > G; c.9403del
9326insA, 6174delT>50% (4,12)

According to a survey, more than 2% of Ascenase Jewish women carry one of the three frequently detected mutations compared to non-Ascenase population with 0.2% frequency. It turned out that ancient founder mutations can also be observed in other populations too.

One of the first data on hereditary breast cancer carrying families was provided from Hungary. Early examinations according to the national databases, one in three hundred new-borns in Hungary carries *BRCA1* or *BRCA2* mutation.

The importance of the identification of a pathogenic *BRCA* mutation for healthy women may be a preventive measure through risk-reducing mastectomy and salpingo-oophorectomy (2). The mutational status in a woman diagnosed with breast cancer may influence treatment and prognosis but also enables the prevention of future cancers. According to the correct Hungarian legislation ***BRCA1/2* genetic testing has been restricted to breast cancer patients** having a high risk of being a carrier.

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Genetic counselling and genetic testing for hereditary cancer syndromes in Budapest Hungary

In case of suspicion of HBOC, a precisely regulated, multistep genetic counselling is required. Carrier status has to be determined by molecular genetic testing of genes to be interested.

The complex professional process involves the individual and family history of the family tree, calculating the probability of the disease, the gene test cost / efficiency reflection and professional discussion, test result communication, planning for close follow-up and possible risk reduction strategies, psychosocial support and protection of personal data.

Many models are known for their different levels of development of a health system in different countries. According to the current Hungarian legislation in force (XXI / 2008 "Genetic Law") in genetic counselling and genetic screening many professions are involved in clinical practice.

The process of genetic testing in a family most often starts with a family member of diagnosis of breast or ovarian cancer. The genetic test offers the best chance of identifying the predisposing hereditary mutation in the family and interpretation of the results carried out for the family members.

The process of genetic counselling

Genetic counselling should be given to high risk hereditary cancer person or yet non-affected individuals during a process of multi-stage, complex communication which is often a serious psychological burden for those seeking an advice. It is important to emphasize that the gene test is only one step of the whole process of genetic comprehensive counselling program only part of the process before and after the test.

Regular genetic counselling includes the risk assessment (pre-test counselling), which is in some cases in the absence of the test indication means the end of counselling.

The so called post-test counselling especially for high-risk individuals is necessary for the appropriate interpretation of the test.

After the risk assessment and providing information to the patient of the nature of the test, the patient must be provided sufficiently enough time to decide whether she agrees and signs the “Consent Statement” which confirms that Genetic Counselling and Genetic Examination has been understood.

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Post-test genetic counselling is presenting the results and these is based on detailed health options (XXI / 2008 "Genetic Law"). Patient's psychosocial support is part of both counselling.

Possibilities of risk assessment

Evaluation of personal cancer risk means both absolute risk calculation as well as the probability of being gene carriers in the family. Detailed personal and 3-4 generations anamnesis are required to set a family tree with standard markings. Description of the patient's own risk contains the individual history the previously identified benign and malignant tumors, the data of menarche, age of first birth, hormonal contraception, time of artificial insemination, hormone replacement, menopause time, lifestyle, and environmental information (alcohol, smoking, special diet, job). The family history should ensure the age of the affected relatives with tumor, which organ was affected and ideally the pathology parameters (such as tumor stage, grade and molecular subgroup), previously used oncological treatment (surgery, chemo-, radio, endocrine therapy). Information on ethnicity should be obtained.

Role of genetic and non-genetic risk factors has been evaluated since 1997 in BRCA1 and BRCA 2 Reference Centers in 42 countries with the participation of Hungary in frame of International BRCA1 and 2 Cancer Cohort Study (IBCCS) by processing data from basic and follow-up questionnaires. The patient involved in genetic counselling has to be prepared for details of the family history, and has to indicate if novel cancer diagnosis appears in the meantime.

Predictive risk assessment

Age, positive family history, early menarche, late menopause, nullparity, late primiparity, all increase the risk of developing a malignant cancer. Models are based on an account of these risk factors that value the risk of malignant cancer in healthy women. Many predictive models are known to assess the high risk of breast cancer (*BRCA1* and *BRCA2* mutation) prior to gene testing. Among the mathematical models the best known are: Gail, Claus, Tyrer-Cuzick, BOADICEA, modified BOADICEA (2008), BRCAPRO, Myriad I / II, and Couch Models. The Claus model is the oldest, in which the cumulative risk of breast cancer

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is estimated by the family history and age by period of 10 year life groups between 29 and 79 years.

In the Claus model, data of heathy relatives in the family concerning number and age of them and relationship with the index person are not taken into consideration which is a serious drawback of this method.

The most widespread model is the Gail model available on the website of the National Cancer Institute (NCI) in the United States. The model's website is used by 20-30 thousand times a month.

The improved BOADICEA model (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) is web-based, validated and continuously developed model is suitable for predicting *BRCA1* and *BRCA2* mutation carrier status. In addition, generation effects can also be estimated.

According to literature, the *BRCA1* and *BRCA2* mutation risk estimation does not produce unwanted psycholocical effects neither in short nor in long term. Positive *BRCA* risk assessment are not associated with higher depression.

The most accurate risk assessment is the genetic testing of the mutation status of *BRCA1* and *BRCA2* genes regarding the likelihood of breast cancer.

The accurate mutation carrier status test allows the risk assessment not only the person affected but also the asymptomatic / healthy family members, too.

Clinical genetic test to detect inherited cancer

Genetic test criteria may vary according to various international or local professional recommendations, statutory regulations, special local populations or mutations (XXI / 2008 Genetic Law) in Hungary.

In accordance with the above, the following conditions are applicable to carry out genetic test:

- a personal or family history of genetic predisposition;
- the test result has an influence on health care in the patient and / or in the family;
- has more benefits than risk;
- the test is voluntary;

Potential benefits and risks should be discussed during the pre-test discussion and the possible alternatives to molecular genetic testing should also be described. The test result

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enables the patient to decide on the preventive measures: tight oncology follow-up and/or chemoprevention and risk reduction surgery. The protection of personal data and personal rights has paramount importance (XXI / 2008 "Genetic Law"). Gene tests are not recommended for individuals under 18 years of age.

4. The situation of the current research Programs on mutation screening and founder mutations detection for HBOC and CCR

Based on: **Oláh E,** Mátrai Z: Herediter emlő- és petefészekrák-szindróma, a gyanútól a rizikócsökkentésig. MC Medicina Chapter 15. 389-408

The first evidence of genetic defects inherited in families can be a reason for some hereditary tumor disorders was suggested by Mary Claire King an American geneticist. The possible site of *BRCA1* (BReastCAncer 1- the first "breast cancer gene") located on the long arm of the 17 th chromosome has been suggested by M.C. King. Discovery of *BRCA2* (BReastCAncer 2- the second “breast cancer”) gene took one more year to be described. Germline mutations in the highly penetrant cancer susceptibility genes, *BRCA1* and *BRCA2* are associated with a high lifetime risk of breast and ovarian cancer. Novel scientific results has been obtained in the last two decades about the function of *BRCA* genes and the risk of *BRCA* induced tumor formation in families carrying *BRCA* mutations.

Gene products of *BRCA* genes interact with different proteins in order to repair double-stranded brakeage of DNA, activation of checkpoints of the cell cycle and participate activation of a response to DNA damage.

Genetic testing related to inherited mutations of *BRCA* genes and risk assessment in framework of genetic counselling makes it possible to identify risk-averse people, thereby promoting early diagnosis, risk reduction, and proper therapeutic decisions. **The Research Group of Professor Edit Olah** joined to an international consortium in 1992 to get insight into the genetic background of hereditary breast and ovarian cancer. **Olah’s group has been providing *BRCA1* and *BRCA2* gene tests for nearly 20 years** for families with hereditary defects in case of more than one breast or ovarian cancer on the same branch of the family or even one male breast cancer and also when

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the diseases are detected especially in young age (under 40 years). Genetic counselling and genetic tests are collaborated by a multidisciplinary team composed of clinical and molecular geneticists, clinical oncologists, breast surgeons, gynaecologists, human genetic assistants, psychologists in **Budapest, Hungary at the Molecular Genetics Department of National Oncology Institute.** The genetic tests are financed by the Hungarian National Health Insurance Company.

Department of Molecular Genetics of National Oncology Institute at the Institute of Health Sciences in Budapest Hungary is the *BRCA1* and *BRCA2* National and International Reference Center for investigations. Nearly **9,000 genetic tests** have been carried out in order to detect hereditary cancers **since 1995**. Hungarian experiences are now demonstrated with a focus on breast and ovarian cancer syndromes.

The incidence and penetrance of BRCA 1 and 2 inherited mutations in Hungary

Ninety- ninety-five percent of breast cancers are not due to the *BRCA1* and *BRCA2* disease causing variants. **In Hungary 5–7% of breast cancers and 15 % of ovarian cancers can be associated with *BRCA1* and *BRCA2* genes with definitive mutations.** However, even hereditary (often with familiar appearance) breast cancers are connected with further somatic mutations and non-genetic factors. A complex, multi-tiered stream of carcinogenesis still remain unknown.

BRCA1 and *BRCA2* genes of germline inheritance with other genetic and environmental factors and lifestyle can possibly be responsible for the hereditary breast and ovarian cancer syndromes (HBOC).

Following features are main indicators for HBOC:

- cumulative incidence of breast or ovarian cancer in a family on the same branch;
- juvenile breast cancer (the most common of hereditary tumors);
- often multi-focal, bilateral or multiple primary tumors can be found in a patient
- other cancers: male breast cancer and rarely prostate, pancreatic cancer;
- Ashkenazi Jewish (Eastern European) ancestry;

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- Triple Negative breast cancers (<60y)

Due to autosomal dominant inheritance there is 50% chance of passing the mutated allel into the offspring. A woman can still be a mutant *BRCA* allel carrier even if never turned on her female branch of the family since the defective allel can be derived from her father's side.

The average cumulative risk of *BRCA1* and *BRCA2* mutation carriers are 56-87% in case of breast cancer and 27-44% of ovarian cancer respectively up to the age of 70 years.

Complete penetrance of *BRCA1* and *BRCA2* mutations cannot be observed so other genetic and environmental factors may also influence the risk of the diseases. Studying gene-environment interactions nowadays are a popular research interest. The cumulative risk of diseases was compared to the randomly selected population involving in Hungarian data: significantly lower risk has been found in the random population than in the disease associated one. According to these studies, the *BRCA1* mutation caused carcinoma risk is in average 65% for breast cancer, 39% for ovarian cancer and *BRCA2* risk is 45% for breast cancer and 11% for ovarian cancer, respectively.

BRCA1 carriers manifest disease at younger (43 year old) age than *BRCA2* mutation carriers (47year old). Edit Olah's working group detected that approximately 90% of *BRCA* mutation carriers develop breast cancer before their age of 50 and there is no difference between *BRCA* mutation's carriers or not being a carriers for ovarian cancer in Hungary.

Breast cancer patients with *BRCA1* or *BRCA2* mutations develop the second primer tumor in the opposite breast have increased risk of approximately with a 3-5% of annual risk which means 17% in 5 years, 30-40% in 10 years.

Danger of contralateral breast cancer development is lower at the age of over 50 years with *BRCA2* mutation than with *BRCA1* mutations.

In Hungary both genes, but especially *BRCA2* are responsible for the relative risk of male carriers for the disease in 6 % . However male breast cancer is rare, *BRCA* caused tumor was found in 0.1-0.2%. According to the Hungarian data (E. Olah) the *BRCA2* mutations are responsible for more than 20% of male breast cancer.

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BRCA1 and *BRCA2* mutation carriers have additional other tumor risks too. Male *BRCA2* mutation carrier HBOC syndrome patients have higher risk of developing prostate cancer under the age of 65 (up to 20 times greater than relative risk to the average population). There is an increased risk of pancreatic cancer, too. The breast cancer of *BRCA1* mutation carriers is mainly called triple negative (estrogen receptor negative, progesteron receptor negative, ERBB2 / HER2 negative) belongs to the basal (CK5 / 6 +) subtype. *BRCA1* mutation is justified in every fourth basal breast cancer. Molecular characteristics of breast cancer of *BRCA2* mutation carriers are practically the same compared to sporadic breast cancer's patients. Although familiar hereditary breast cancer syndromes are the most commonly occurring because of *BRCA1* and *BRCA2* inherited mutations (> 80%), but other hereditary syndromes can also be associated with increased level of breast and ovarian cancer risk.

Besides the *BRCA* mutations, high risk of breast cancer is associated with *TP53, PTEN, STK11, CDH1* hereditary gene mutations carrying allels in the germ line. The rest of potential breast cancer predisposing genes have unknown frequency and only a moderate (2-3-fold) risk-increasing effect.

The aforementioned genes of rare cancer syndromes take place in less than 1% compared to breast cancer families. Mutation spectrum of *STK11* gene has been published from colon polyps and malignomas affected Hungarian families. Beside *STK11* and *BRCA1, BRCA2,* other genes have already been suggested for familiar adenomatosis polyposis syndrome like *APC, ATM, BAP1, BARD1, BMPR1A, BRIP1, CDH1, CDKN2A CDK4, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH6, MITF, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4,* and *TP53***.** The role of *STK11* gene of breast cancer at young age has been studied and currently being evaluated at the Molecular Genetics Department of National Oncology Institute.

The Lynch syndrome (also called hereditary nonpolyposis colorectal cancer, HNPCC) is also characterized in this Institute since HNPPC and ovarian cancer might appear together.

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The mutations of HNPCC /Lynch syndrome's gene called *EPCAM / TACSTD1* have been discovered and also first published by E. Olah's team in Hungary. Twenty-five -thirty percent of familiar breast cancer carcinoma can be explained by the so-called "breast cancer genes" known today, however some predisposing genes are still hidden.

Together with CIMBA (Consortium of Investigators of Modifiers of *BRCA 1* and *BRCA2*) many new predisposing genes and population specific frequent variants have also been published by E. Olah. These variants are low risk variants but combined their occurrence can significantly change *BRCA1* and *BRCA2* risk carriers.

5. List of Institutions, Cancer Centers that provide genetic testing and councelling services

1. Molecular Genetics Department of National Oncology Institute, Budapest, Hungary

6. The situation of education programs regarding Oncogenetics

Education of Oncogenetic is briefly included in the subjects of either Oncology or Clinical Genetic courses for undergraduate studies of Medical Universities. It would be important to strengthen the ongogenetic training not only at the level of undergraduate studies but also for postgraduate level too.

There is a need to organize a good training program for Oncological license exam with oncogenetic specifities or Clinical Genetic Board Exam with special oncogenetic training.

7. Identification of the practical needs (infrastructure, human and financial resources in order to estabilish and to develop an Oncogenetic Network

The minimal requirements expected of oncogenetic laboratories: (similar in each country)

a) DNA extraction area (pre-PCR area), corresponding to the following activities:

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1. Receiving and processing biological samples (periphereal blood / tissue)
2. DNA extraction by saline, non-enzymatic and non-toxic methods
3. DNA quantification and purity evaluation by spectrophotometry
4. DNA dilutions and aliquoting in a DNA biobank
5. DNA storage as a biobank

Required equipment:

- Laminar hood, HePa filter
- Cooling centrifuge for 50 ml tubes and 96-well plates
- Cooling centrifuge for 1,5 ml and 0,2 ml tubes
- Vortex mixer
- Adjustable thermoblocks and Adjustable temperature waterbath
- UV- spectrophotometer for small volumes measurement
- Adjustable micropipettes
- 4C fridges, -20C freezers

b) PCR amplification and DNA sequencing area

- Dilution of all reagents
- PCR amplification mixes and reactions
- Migration of PCR products by agarose gel electrophoresis and visualization
- Amplicon purification by enzymatic non-toxic methods
- DNA sequencing mixes and reactions (dye terminator, Sanger method)
- DNA sequencing products purification by resin, non-toxic methods

Required equipment:

- Cooling centrifuge for 96-well plates
- Cooling centrifuge for 1,5 ml and 0,2 ml tubes
- Thermal cycler with dual block (2 x 96-well plates)
- Real-time thermal cycler
- Vortex mixer
- Adjustable thermoblocks

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- Adjustable temperature waterbath
- Adjustable micropipettes, multi-channel micropipettes, adjustable volume dispensers
- 4C fridges, -20C freezers

c) Capillary electrophoresis / interpretation area

Preparing of 96-well plates for capillary electrophoresis

- Loading of 96-well plates on capillary sequencer (genetic analyzer)
- Capillary electrophoresis
- Data processing and export
- Data import and interpretation
- Elaboration of molecular diagnostic test results

Required equipment:

- Cooling centrifuge for 96-well plates
- Capillary sequencer (genetic analyzer)
- Adjustable micropipettes, multi-channel micropipettes, adjustable volume dispensers
- 4C fridges, -20C freezers
- Desktop computer with appropriate software for data interpretation

Human resources requirement:

- Molecular biologist as diagnostic responsible (post-doc or higher) : 1
- Molecular biologist as workflow responsible (Masters degree or higher) : 1
- Biologist / biochemist for main workflow : 2
- Laboratory staff : 1
- Cleaning staff : 1

Typical diagnostic workflow:

1. DNA extraction by saline, non-enzymatic and non-toxic methods

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2. DNA quantification and purity evaluation by spectrophotometry
3. DNA dilutions and aliquoting
4. Mutation pre-screening for recurrent mutations (PCR-based techniques)
5. PCR amplification
6. Migration of PCR products by agarose gel electrophoresis and visualization
7. Amplicon purification
8. DNA sequencing (dye terminator, Sanger method)
9. DNA sequencing products purification
10. Capillary electrophoresis
11. Data processing and export
12. Data import and interpretation
13. Elaboration of molecular diagnostic test results

Financial needs estimate:

- Equipment: EUR 150.000
- Reagents: EUR 3000 /index case sample and EUR 100 / mutation verification in relatives sample

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