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Moving from NIPT to cancer screening

universality of low pass whole-genome analysis

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Assoc. prof. Tomas Szemes, PhD.

Non-invasive screening milestones

Pregnancy → Spatially and Temporally limited

- Uterus
- 9 month from conception
- reproductive age (age 12-45)

1959
Zipursky A, et al.
Fetal cells in maternal blood

1969
Walknowska J, et al.
Karyotypic analysis of fetal lymphocytes in maternal blood

1997
Lo YM, et al.
Presence of fetal DNA in maternal plasma

2011
Non-invasive fetal trisomy (NIFTY) test
The first NIPT test approved

1869
Ashworth T
Circulating tumor cells in blood

1948
Mandel P and Métais P
Cell-free nucleic acids in plasma

1977
Leon SA, et al.
Higher cfDNA concentration in cancer patients

1994
Sorenson GD, et al.
Mutated *K-ras* in plasma cfDNA of cancer patient

2016
cobas EGFR Mutation Test v2
The first liquid biopsy test approved

Cancer → „Anytime Anywhere“

Non-invasive prenatal test development

RESEARCH ARTICLE

Utilization of Benchtop Next Generation Sequencing Platforms Ion Torrent PGM and MiSeq in Noninvasive Prenatal Testing for Chromosome 21 Trisomy and Testing of Impact of *In Silico* and Physical Size Selection on Its Analytical Performance

Gabriel Minarik^{1,2,3*}, Gabriela Repiska¹, Michaela Hyblova², Emilia Nagyova², Katarina Soltys², Jaroslav Budis⁴, Frantisek Duris^{2,4}, Rastislav Sysak⁵, Maria Gerykova Bujalkova^{6,7}, Barbora Vikova-Izrael^{1,3}, Orsolya Biro⁸, Balint Nagy⁸, Tomas Szemes^{2,3}



PLOS ONE

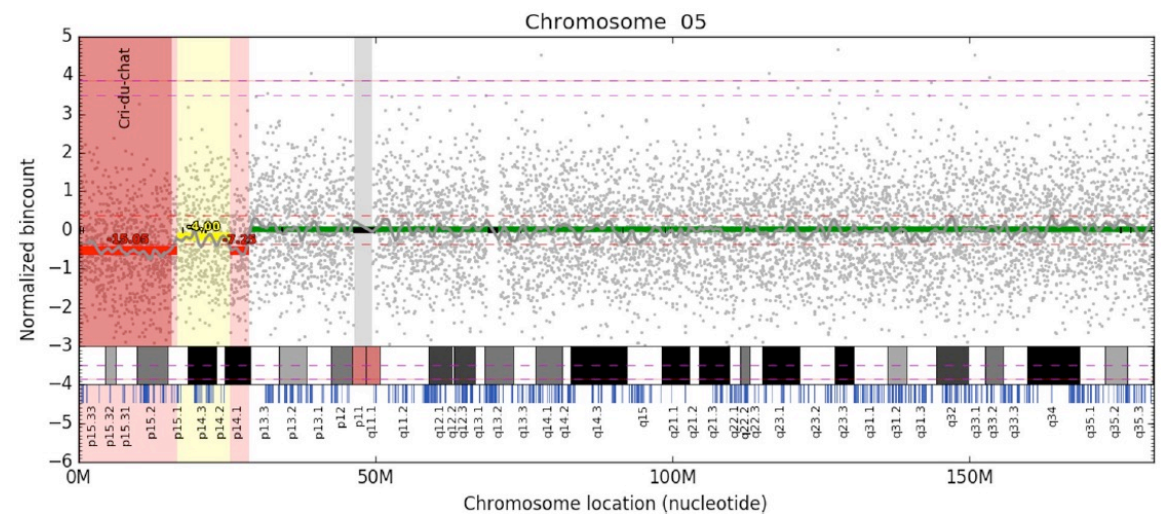
RESEARCH ARTICLE

Non-invasive prenatal testing (NIPT) by low coverage genomic sequencing: Detection limits of screened chromosomal microdeletions

Marcel Kucharik^{1,2}, Andrej Gnip^{3,4}, Michaela Hyblova^{3,4}, Jaroslav Budis^{1,2,5}, Lucia Strieskova¹, Maria Harsanyova^{1,6}, Ondrej Pös^{1,6}, Zuzana Kubiritova^{1,6,7*}, Jan Radvanszky^{1,7}, Gabriel Minarik^{3,4}, Tomas Szemes^{1,2,6}



- Development started at **2013**
- Clinical use since **2015**
- Low-coverage whole-genome sequencing
- Fetal **Aneuploidies** and **Sub-chromosomal** aberrations
- Validated for: Fetal CNVs ≥ 600 kbp
Maternal CNVs ≥ 200 kbp



Parallels between Fetus and Tumor development

F1000Research

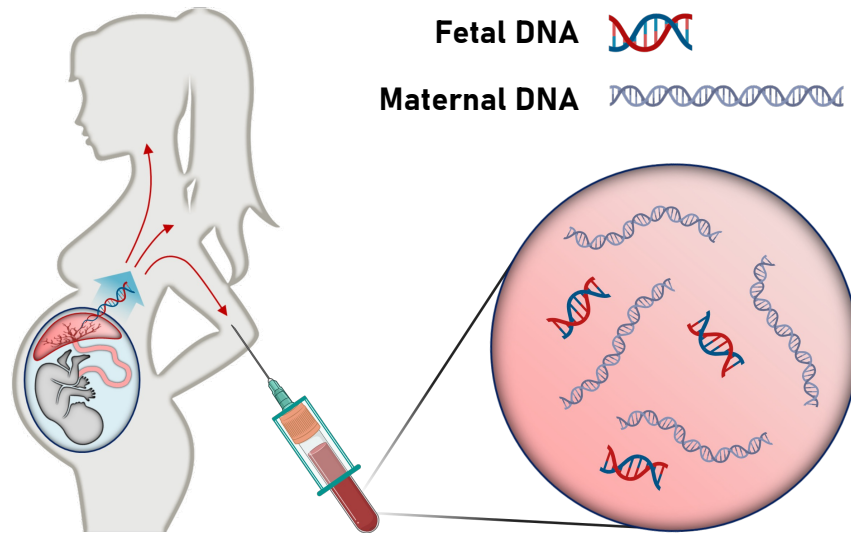
F1000Research 2019, 8(F1000 Faculty Rev):764 Last updated: 31 MAY 2019



REVIEW

Recent trends in prenatal genetic screening and testing [version 1; peer review: 2 approved]

Ondrej Pös¹, Jaroslav Budiš², Tomáš Szemes^{1,2}



- Trophoblast apoptosis → **cffDNA** (≤ 150 bp)
- Concentration → 7.8% – 13% after ~10th week of gestation
- Influencing factors: BMI, obesity, placental mass
- Standard in developed countries

European Journal of Human Genetics (2018) 26:937–945
<https://doi.org/10.1038/s41431-018-0132-4>

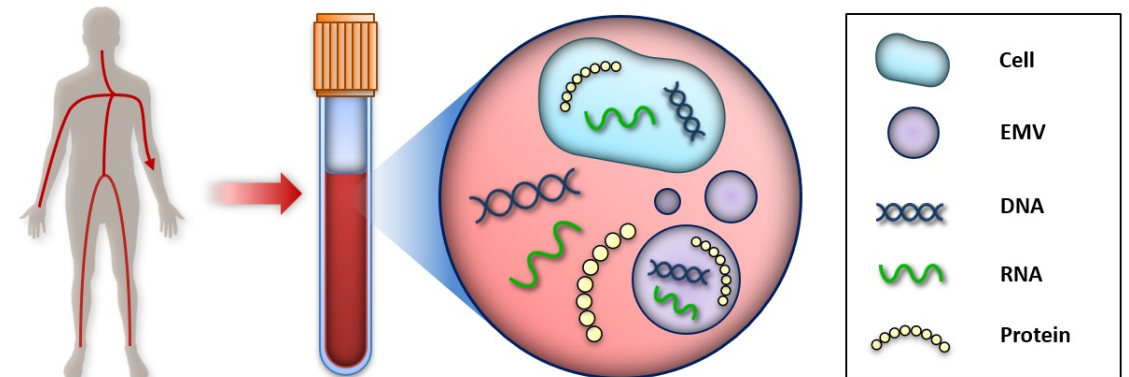


REVIEW ARTICLE



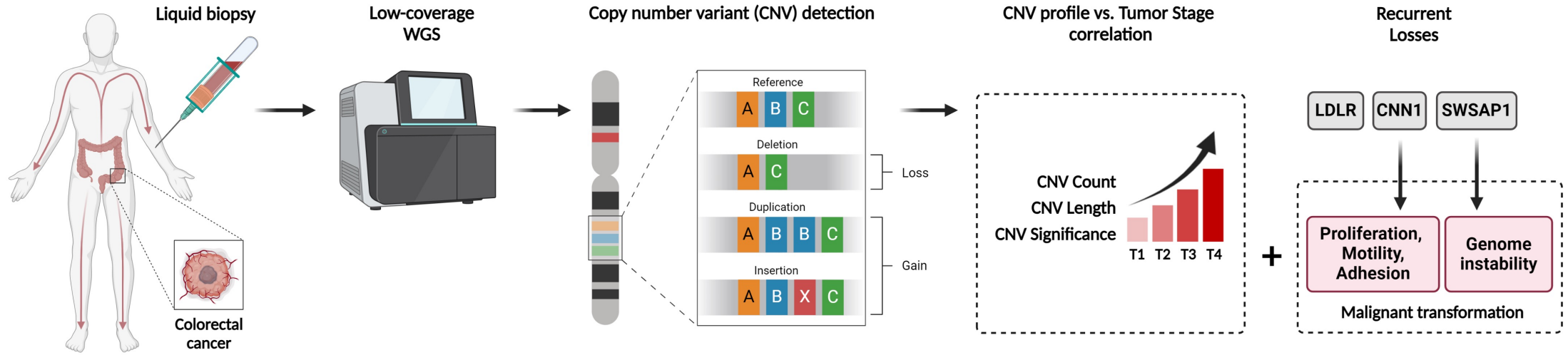
Circulating cell-free nucleic acids: characteristics and applications

Ondrej Pös¹ · Orsolya Biró² · Tomas Szemes¹ · Bálint Nagy^{1,3}

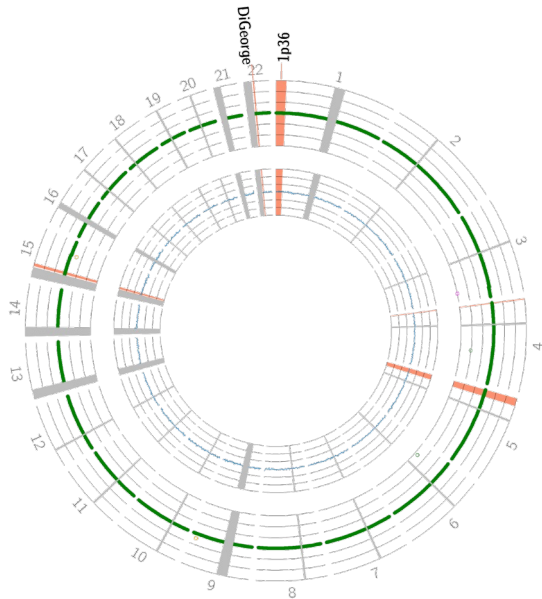


- Hematopoietic cells apoptosis → **cfDNA** (166 bp)
- Tumor cells necrosis → **ctDNA** (< 145 bp)
- ctDNA concentration 1% – 10% of total cfDNA
- Influencing factors: Physiological and Pathological aspects
- Single cancer tests are available

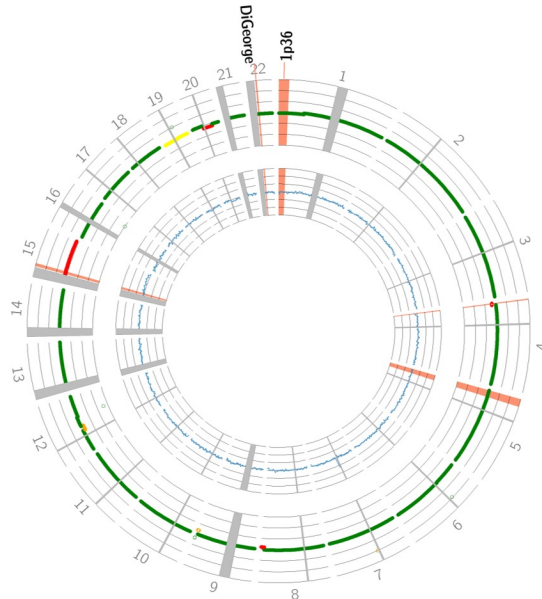
NIPT to cancer screening workflow adaptation



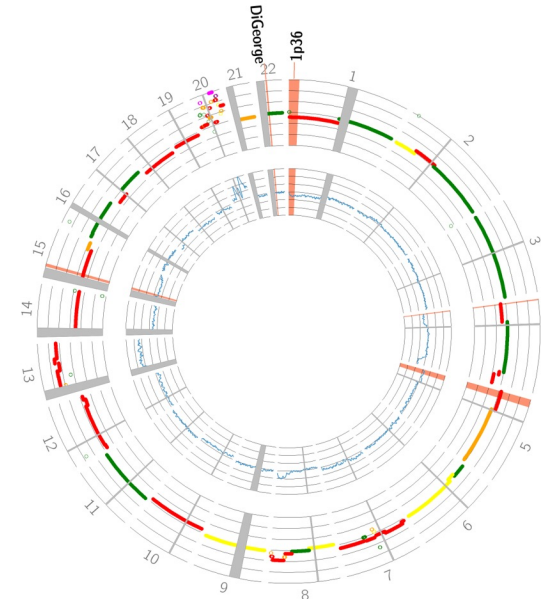
Healthy (1 Dup / 2 Del) 3 CNV



GIST_081: Stage T1; (2 Dup / 7 Del) 9 CNV



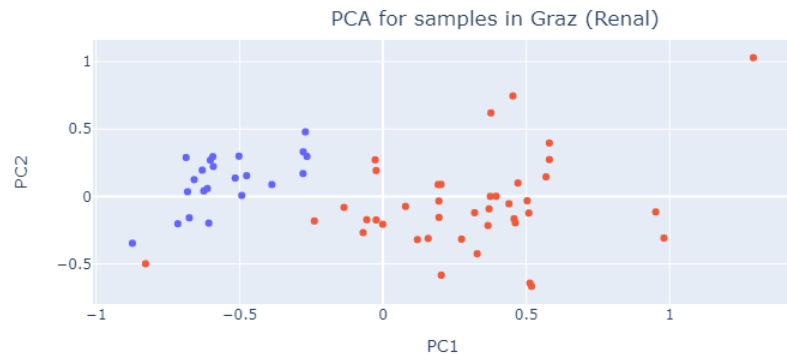
GIST_056: Stage T4; (38 Dup / 23 Del) 61 CNV



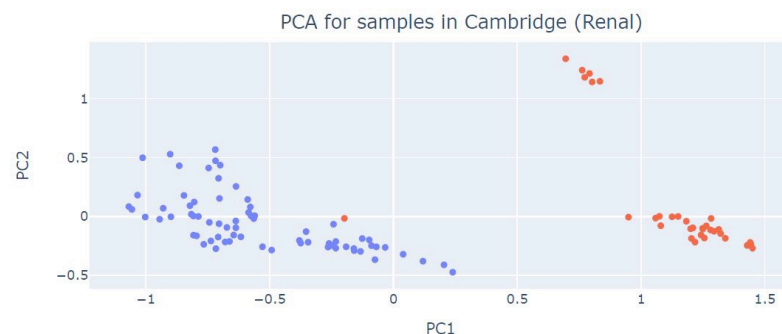
Increment of mutation spectrum and cfDNA characteristics



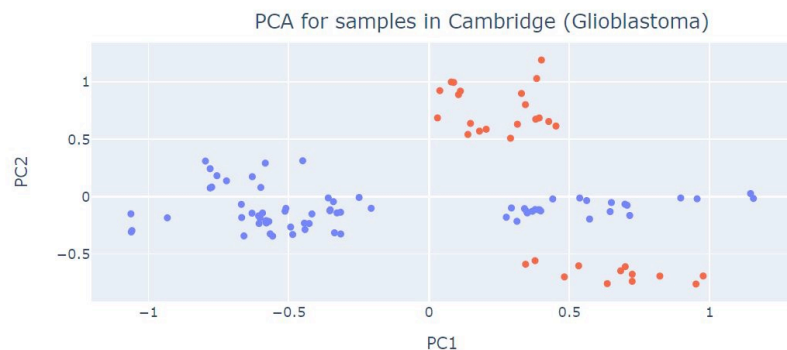
Samples:
 ● 43 Renal cancer
 ● 22 Healthy



Samples:
 ● 33 Renal cancer
 ● 65 healthy



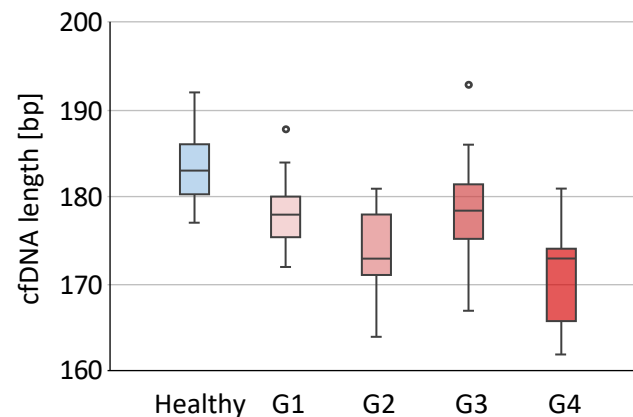
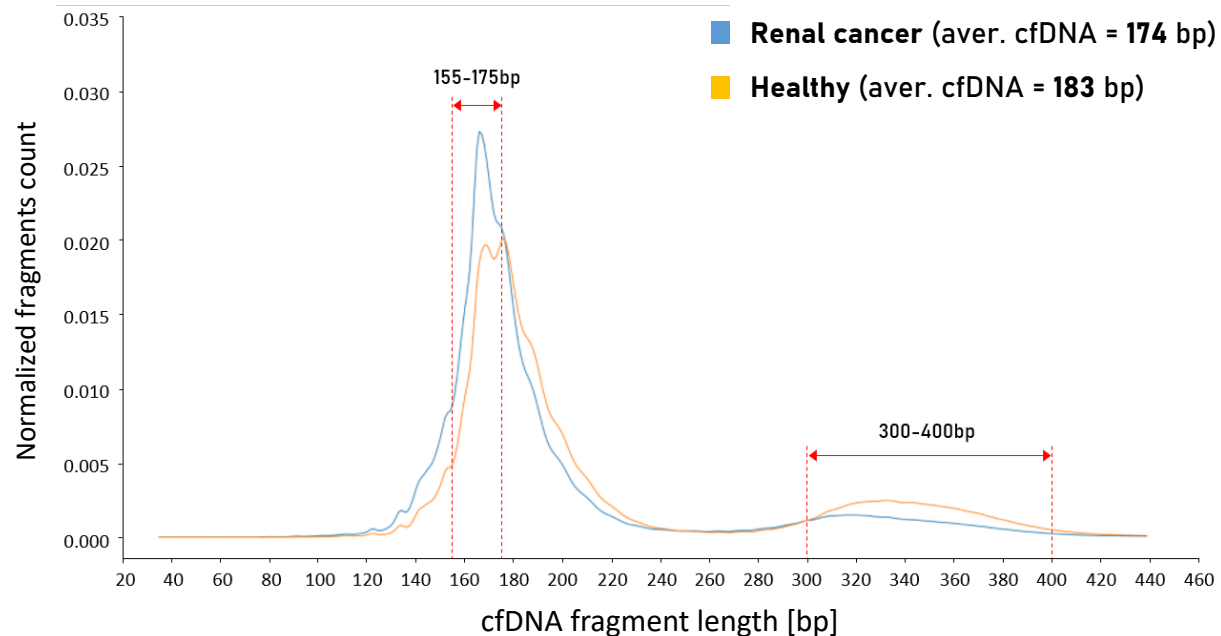
Samples:
 ● 34 Glioblastoma
 ● 65 healthy



Lengths of circulating DNA fragments as a promising predictor of cancer stage

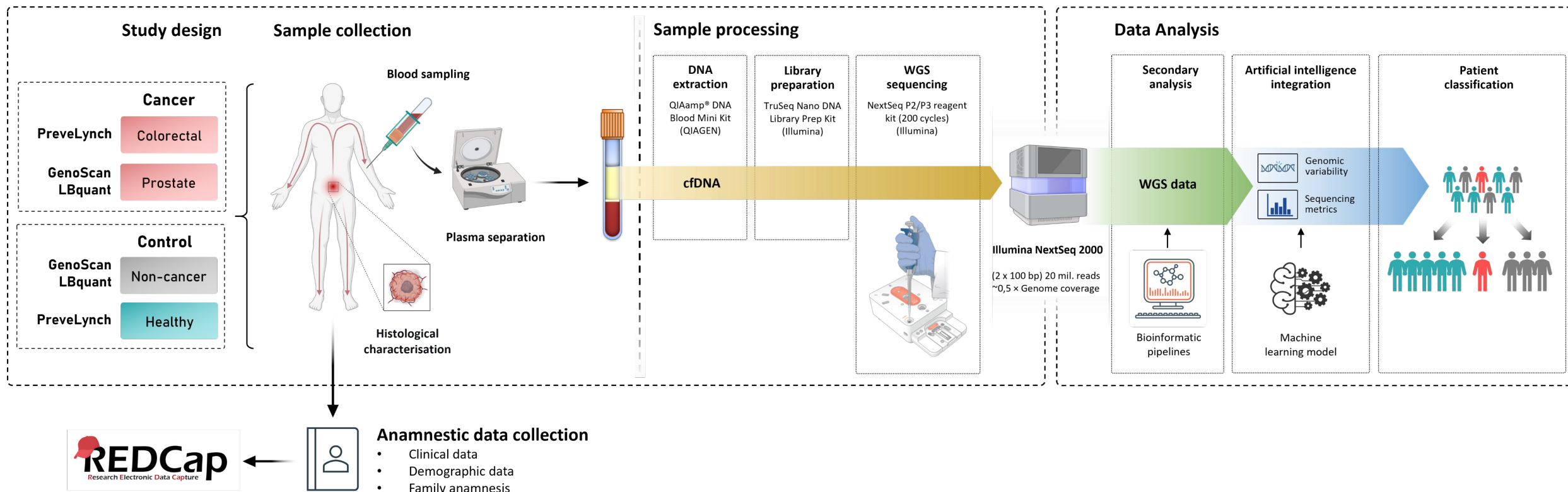
Marek Štrba^{1,2}, Jaroslav Budiš^{1,3,4}, Werner Krampf^{1,3,5}, Tomáš Sládeček¹, Ondrej Pös^{1,3,5},
 Mária Lucká^{6,7}, Tomáš Szemes^{2,3,5}

NewsLab, 2021; roč. 12 (2): 58 – 63



Samples:
 ○ 43 Renal cancer
 ○ 22 Healthy

... and the study was born



Performance of explainable AI in cancer prediction

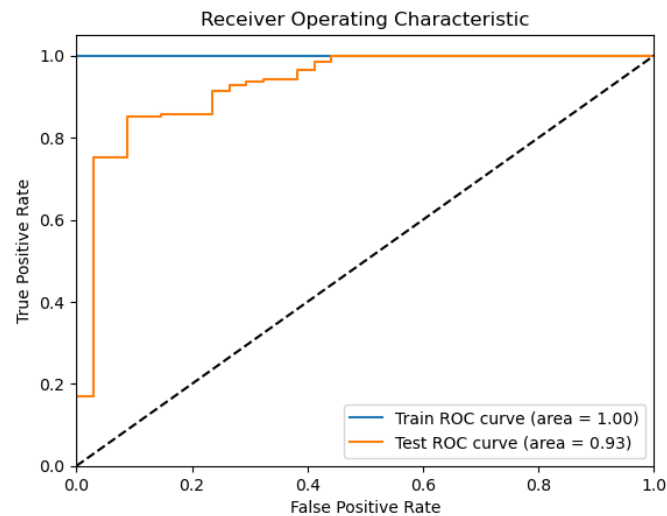
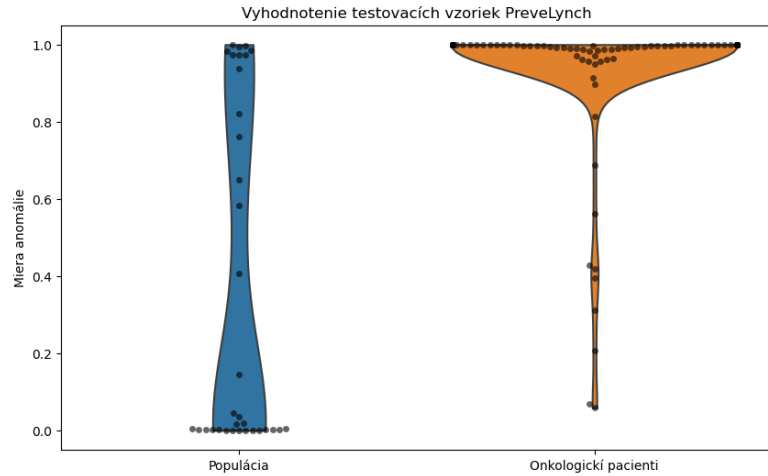
- 160 parameters (genomic variability + sequencing metrics)
- 108 **Colorectal cancer** (CRC) patients *vs.* 474 controls

Training:

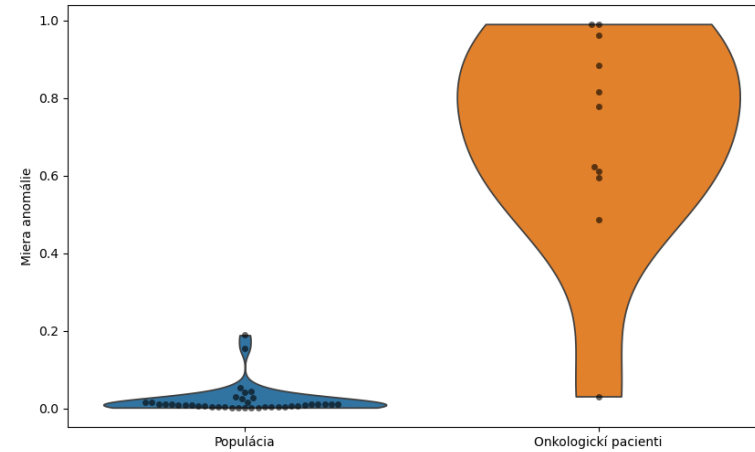
- 74 CRC
- 333 Controls

Testing:

- 34 CRC
- 141 Controls



- 671 parameters (genomic variability + sequencing metrics)
- 60 **Prostate cancer** patients *vs.* 369 controls

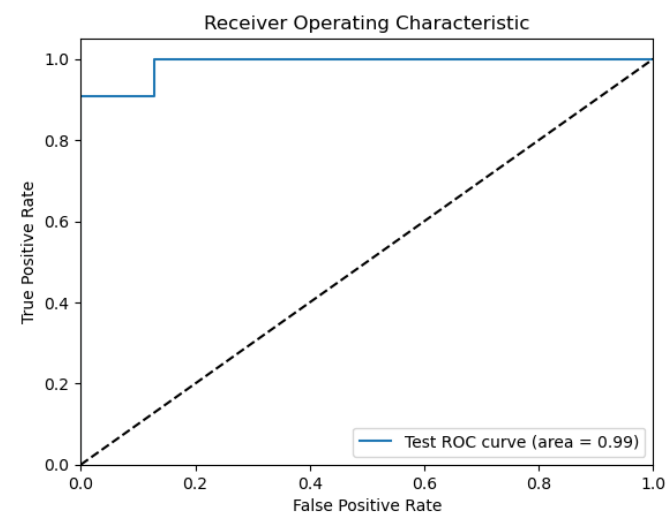


Training:

- 49 Prostate
- 330 Controls

Testing:

- 11 Prostate
- 39 Controls



Interference with cfDNA profile

Methodological aspects



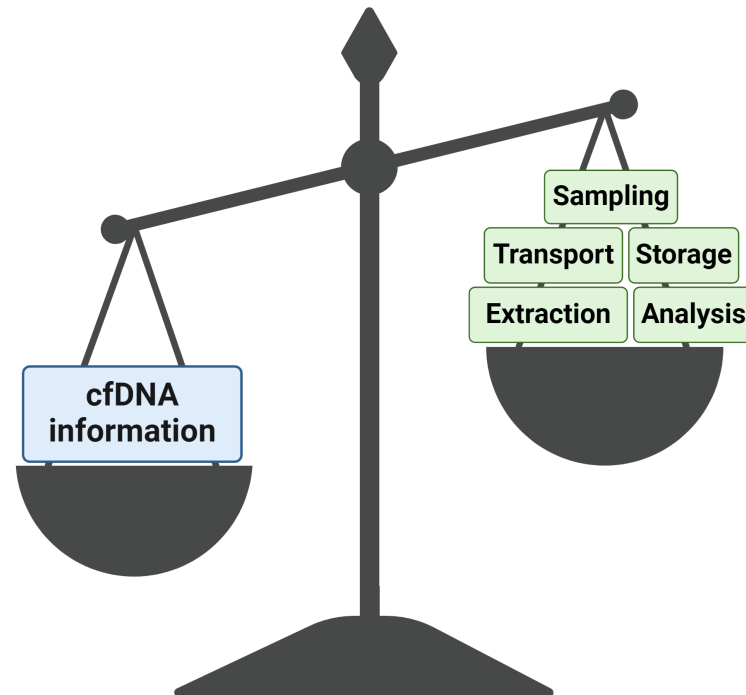
International Journal of
Molecular Sciences

Int. J. Mol. Sci. 2020, 21, 8634; doi:10.3390/ijms21228634

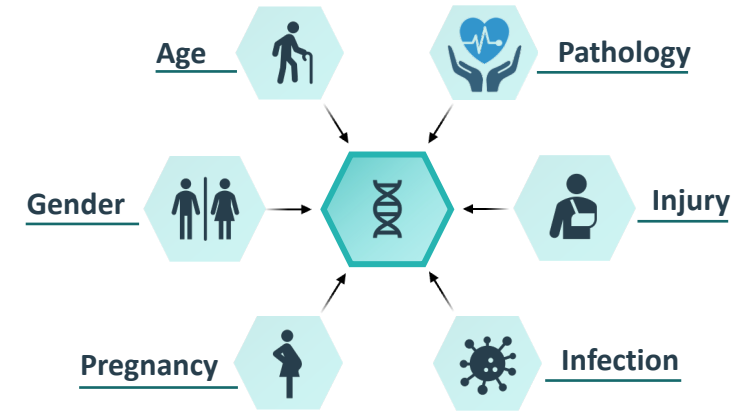
Review

Technical and Methodological Aspects of Cell-Free Nucleic Acids Analyzes

Zuzana Pös^{1,2,3}, Ondrej Pös^{2,3,4}, Jakub Styk^{4,5}, Angelika Mocova^{1,2}, Lucia Strieskova³, Jaroslav Budis^{3,4,6}, Ludevít Kadasi^{1,2}, Jan Radvanszky^{1,2,4,*} and Tomas Szemes^{2,3,4,*}



Physiological and pathological aspects



- Median age at cancer diagnosis → 60-70
- 95% of adults 60+ have at least one Chronic condition



Hypertension
(High Blood Pressure)
60%



High Cholesterol
51%



Arthritis
35%



Ischemic /
Coronary
Heart Disease
29%



Diabetes
27%



Chronic Kidney
Disease
25%



Heart Failure
15%



Depression
16%



Alzheimer's
Disease and
Dementia
12%



Chronic
Obstructive
Pulmonary
Disease
11%

Conclusions



Single cancer screening

Several tests available ←

Single purpose ←

Cheaper per test ←

Multi-cancer screening

→ So far challenging

→ More beneficial health-related information

→ Overall time and cost savings

□ Acknowledgments

PreveLYNCH [ITMS: 313011V578]

Long-term strategic research and development focused on the occurrence of Lynch syndrome in the Slovak population and possibilities of prevention of tumors associated with this syndrome

GenoScan LBquant [ITMS: NFP313010Q927]

Introduction of an innovative test for screening and monitoring of cancer patients

INCAM [APVV-21-0296]

Identification of novel biomarkers linked to the relapse of metastatic colorectal cancer after metastasectomy

SEPMIN [ITMS: 313021BUZ3]

Early identification of pathogens in sepsis using third generation real-time nanopore sequencing



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