RESEARCH TOPIC MECM_6

Diagnosis of tubal malignant ovarian cancer precursor lesion through the analysis of DNA from Pap test smear

Curriculum

MECM Standard

Research Area

Onco

Laboratory name

Laboratory of Cancer Pharmacology

Research Supervisor

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Abstract

A significant number of women with germline pathogenic variants in BRCA genes (gBRCA) have high risk to develop High-Grade Serous Epithelial Ovarian Cancer (HGS-EOC), 40% for women with BRCA1 mutation and 20% for BRCA2 mutation to age 80. Risk-reducing surgery (salpingo-oophorectomy) is universally recommended from the age of 35 for BRCA1 heterozygotes and from the age of 40 for BRCA2 heterozygotes. The pathological analysis of the fallopian tubes of women undertaking prophylactic surgery, shows early neoplastic lesion known as serous tubal intraepithelial carcinomas (STICs) in only 5% of cases. Unfortunately, there are no sensitive and non-invasive methods to detect STICs, making it difficult to determine when prophylactic surgery should be performed. We have recently shown that HGS-EOC can be detected up to 9 years before diagnosis by examining the genomic instability profile (Copy number Profile Abnormality, CPA) of DNA purified from Pap test smears. The sensitivity of our test was 75% and the specificity 96%, suggesting the potential use of CPA score for early detection of HGS-EOC (Paracchini et al., Science Translational Medicine 2023). The analysis of other variables (methylation status, type of BRCA variants and clinical features) might further increase the predictive accuracy our test.

Main technical approaches

Technical approaches

- Execute Next-Generation Sequencing (NGS) analyses on biological samples (mainly Thin prep and conventional Pap test specimens), overseeing the entire process from nucleic acid extraction and library construction to downstream data analysis.
- Perform comprehensive genomic and epigenomic profiling.
- Coordinate with pathologists and clinicians for the identification and retrieval of retrospective clinical samples.

Required qualifications and competencies

- Master's degree (or equivalent) in Biotechnology, Biological Sciences, or a closely related discipline.
- Proven practical experience in molecular biology techniques; prior exposure to NGS workflows and associated data analysis is highly preferred.
- Demonstrated ability to independently manage laboratory activities while contributing effectively within a multidisciplinary team comprising biologists, bioinformaticians, statisticians, pathologists and clinicians.

Scientific references

1. Paracchini L, Mannarino L, Romualdi C, Zadro R, Beltrame L, Fuso Nerini I, Zola P, Laudani ME, Pagano E, Giordano L, Fruscio R, Landoni F, Franceschi S, Dalessandro ML, Canzonieri V, Bocciolone L, Lorusso D, Bosetti C, Raspagliesi F, Garassino IMG; TOWARDS group; D'Incalci M, Marchini S. Genomic instability analysis in DNA from Papanicolaou test provides proof-of-principle early diagnosis of high-grade serous ovarian cancer Sci Transl Med. 2023 Dec 6;15(725):eadi2556. doi: 10.1126/scitranslmed.adi2556

2. Paracchini L, Pesenti C, Delle Marchette M, Beltrame L, Bianchi T, Grassi T, Buda A, Landoni F, Ceppi L, Bosetti C, Paderno M, Adorni M, Vicini D, Perego P, Leone BE, D'Incalci M, Marchini S, Fruscio R. Detection of TP53 Clonal Variants in Papanicolaou Test Samples Collected up to 6 Years Prior to High-Grade Serous Epithelial Ovarian Cancer Diagnosis. JAMA Netw Open. 2020 Jul 1;3(7):e207566. doi: 10.1001/jamanetworkopen.2020.7566

3. Pesenti C, Beltrame L, Velle A, Fruscio R, Jaconi M, Borella F, Cribiù FM, Calura E, Venturini LV, Lenoci D, Agostinis F, Katsaros D, Panini N, Bianchi T, Landoni F, Miozzo M, D'Incalci M, Brenton JD, Romualdi C, Marchini S. Copy number alterations in stage I epithelial ovarian cancer highlight three genomic patterns associated with prognosis. Eur J Cancer. 2022 Aug;171:85-95. doi: 10.1016/j.ejca.2022.05.005

4. Potente S, Boscarino D, Paladin D, Marchini S, Beltrame L, Romualdi C. SAMURAI: shallow analysis of copy number alterations using a reproducible and integrated bioinformatics pipeline. Brief Bioinform. 2024 Nov 22;26(1):bbaf035. doi: 10.1093/bib/bbaf035

5. Arildsen NS, Martin de la Fuente L, Måsbäck A, Malander S, Forslund O, Kannisto P, Hedenfalk I. Detecting TP53 mutations in diagnostic and archival liquid-based Pap samples from ovarian cancer patients using an ultra-sensitive ddPCR method. Sci Rep. 2019 Oct 29;9(1):15506. doi: 10.1038/s41598-019-51697-6

Type of contract

PhD scholarship of € 21.000 gross per year awarded by Humanitas University. This sum is exempt from IRPEF income tax according to the provisions of art. 4 of Law no. 476 of 13th August 1984 and is subject to social security contributions according to the provisions of art. 2, section 26 and subsequent sections, of Law no. 335 of 8th August 1995 and subsequent

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modifications.

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