research on patient users showed that certain aspects of FHL could be executed more effectively, to include increased opportunity for personalization of the web interface and risk messaging. FHL version 3.0 is under development and will allow for 1) automatic integration and updating of professional guidelines (e.g. NCCN guidelines for hereditary cancer); 2) expansion as a mobile application and for EPIC electronic health record integration; and 3) capacity to deliver tailored, evidence-based risk messages.

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Two novel APC deletions resulting in a hybrid APC-SRP19 transcript with high sequence homology to U2AF35 splicing factor

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Germline mutations in the APC gene are the underlying cause of familial adenomatous polyposis (FAP), an autosomal dominant syndrome characterized by the presence of multiple colorectal (CRC) adenomatous polyps. Although truncating mutations in the APC gene are the most common defects in FAP patients, recent papers indicate that in a significant number of cases the disease develops due to large deletions that cannot be detected with routine testing. Here we describe two novel germline large deletions of the APC gene detected in 4 unrelated families presenting a severe FAP phenotype. The deletions were characterized using MLPA, high-resolution array-CGH and bridging-PCR followed by Sanger sequencing methodologies. Both deletions (123.466bp and 139.889bp) had a 5' breakpoint in intron 4 of the APC gene and a 3' breakpoint in intron 4 of the SRP19 gene, indicating that these regions are prone to recombination errors and might also be frequently affected by somatic rearrangements in sporadic CRC. RT-PCR analysis showed that the deletions resulted in the production of a hybrid APC-SRP19 transcript with an ORF of 550 AA, with ~92% sequence homology with the ZRSR2 gene. The ZRSR2 gene codes for the U2 small nuclear ribonucleoprotein auxiliary factor 35kD subunit-related protein-2, which plays an important role in RNA splicing. Mutations in this gene have been found in various hematological malignancies associated with poor overall survival. We describe the detection of a potentially novel biomarker that can be used both as a marker for early detection and a target for individualized therapy in CRC patients.

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Investigating the role of *CD44v6* in Gastric Cancer: development of exon-v6 skipping models by CRISPR/Cas9

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Introduction: Gastric cancer (GC) is the 5th most common cancer and 3rd with highest mortality. Standard of care for advanced disease is conventional chemotherapy. CD44v6-containing isoforms are de novo expressed in GC, are often correlated with cancer aggressiveness, and may predict chemotherapy response in vitro. Whether expression of CD44v6-containing variants, or presence of exon-v6 per se in these isoforms, determine tumor behavior and therapy response is unknown. This is relevant for therapeutic design and constitutes our main aim.

Materials and Methods: Using CRISPR/Cas9, we specifically deleted exon-v6, whilst maintaining the reading frame, from two GC cell lines endogenously expressing CD44v6. Edited cell lines were characterized and treated with cisplatin and 5-fluorouracil. Cell survival was compared to *wt* controls.

Results: We obtained homozygous edited cell lines lacking exon-v6 that maintained expression of remaining CD44 variant portions. Edited cells' transcripts resulted *in frame* v5-v7 splicing, mimicking complete exon-v6 skipping. Drug treatments' results demonstrate that removing specifically exon-v6 does not affects GC cells chemotherapy response, however, skipping exon-v6 is sufficient to impair GC cells self-renewing and decrease proliferation levels. Moreover, CD44v6-containing isoforms knockdown modulates cell survival in GC cells.

Conclusions: We successfully designed exon-v6 skipping models in GC cells lines. These exon skipping models are extremely important to disclose exon-v6 specific role in GC chemotherapy response. We conclude that CD44v6-containing isoforms modulate cell survival in GC cells and, furthermore, exon-v6 is capable of, by itself, altering one of