The valorization potential of DEST*IN*CT is three-fold:

1. Optimized GWAI screening protocol
Without adequate and meticulously described standards for (integrated) epistasis analysis we risk the accumulation of false-positives arising from such studies. This would negatively affect the translation of genomic research findings into the clinical diagnostic setting and delay biological understanding of disease. Whereas epistasis studies using SNPs may provide panels of modifier variants (DEST*in*CT WP1,3), sequencing offers the promise of identifying the variants driving epistasis signals (DEST*in*CT WP2). We believe that acknowledging the spatial and functional landscape of the genome and epigenome (DEST*in*CT WP2), and moving away from single markers as primary units of analysis, will improve the transition from statistical findings to instruments with clinical utility.

2. Optimized validation procedures
The optimization of analytic tools proposed in this project proposal goes hand in hand with the optimization of validation procedures.
In clinical diagnostics or prognostics applications, reproducibility in independent data sets is mandatory. Validation success can statistically be investigated within a meta-analysis framework. The lack of such a framework that encompasses the diversity of analytic tools for epistasis analysis motivates WP3 of DEST*in*CT.
Although a number of different approaches of both data-mining and laboratory tools exist, only a few have been applied in functional studies to validate epistasis findings. Moving from localization to function (gene or regulatory elements) is essential to explain molecular mechanisms playing a role in disease. Biological or functional validation procedures may rely in part on a systematic epistasis literature review and structured knowledge from databases that integrates data from a variety of experimental platforms (e.g. Cytoscape, CPDB (ConsensusPathDB-human), GeneMANIA, BioGraph, IMP (Integrative Multi-species Prediction) web server, TRANSFAC® Professional database and MatchTM tools, MatrixCatch tool, etc.). Hence, biological or functional validation procedures may also rely on model organisms.
Alternatively, methods are developed that lead to improved biological insights, as is expected by integrating omics data (DEST*in*CT WP2) or by building statistical epistasis networks from GWAI results. In such networks, nodes represent genes and (weighted) edges represent (the strength of) statistical gene-gene interactions. The approach assumes having aggregated information about gene-gene interactions, and is promising, since it allows the detection of higher-order (>2) interactions by closely investigation genetic attributes that cluster together in the network. Investigating how to best combine statistical and biological validation strategies is seen as a natural follow-up to the work plan described in this project proposal.

3. Personalized medicine
Clinical whole-exome sequencing is increasingly being used for diagnostic evaluation of patients with suspected genetic disorders. A by-product of DEST*IN*CT is that (integrated) strata of individuals are obtained with increased / decreased disease risk (DEST*in*CT WP2). Future investigation of these strata may give leads to define targeted groups for disease management.

The valorisation potential of DEST*in*CT is transferable to 2-DEST*in*CT, the renewal of DEST*in*CT, though initial themes are considered from the viewpoint of "multiplicity". In this section, we concretize the valorisation potential of (2-)DEST*in*CT, while identifying the following real-life contexts in which the project's results can be translated:

1. Identification of common disease susceptibility genes

Rare variants are more abundant in the human genome than common variants; they are worth investigating as they are expected to harbour most of the deleterious mutations. However, commonly adopted study designs involving cases and controls are often underpowered (< 10000 individuals) to detect disease associations with rare variants. This suggests expanding our views and reconsidering alternative study designs such as a) geographically confined study populations, b) family-based designs, and c) multivariate trait studies. Even when restricting attention to geographically confined regions, so-called fine structure may exist and its (non-linear) impact on the identification of disease susceptibility genes (whether through 1D or 2D analyses) needs to be assessed (DEST*in*CT WP1,2). Family-based designs can potentially enrich a sample in rare variants, for which the effect would remain hidden at the population level. MB-MDR was extended before to family-based designs, by first regressing out the family-structure and then submitting the thus obtained residuals as new traits to classic MB-MDR. Family structure is a particular example of a multivariate structure. Therefore, the developments in 2-DEST*in*CT WP2 for multivariate traits are expected to be useful in the context of family-based designs as well.

An increasing number of examples exist where integrated analyses have led to the identification of novel disease genes. The term "integration" is often loosely used though. Two extreme integrative analyses routes are pooling all data prior to analysis (concatenation) and analysing the data sources separately prior to deriving an integrative interpretation. In (2-)DEST*in*CT, we take the middle road by pooling different omics data sources at the gene level, hereby reducing the complexity of potential relationships between genomics, epigenomics and transcriptomics to acknowledge for (DEST*in*CT WP2, 2-DEST*in*CT WP1).

2. Identification of rare disease characterizing genes

There are thousands of rare diseases, defined as diseases which affect a small number of people compared to the general population (in Europe: a rare disease affects 1 out of 2000 individuals). One such are disease is pancreas cancer. Its death rates are rising while death rates for most other cancers continue to decrease in Europe. For pancreas cancer, remarkable progress has been made through omics integration efforts, in particular in disentangling disease heterogeneity. The latter has been achieved by hunting for *ome-wide* reclassifications of disease. The gene-centric approach adopted in DEST*in*CT involves developing *gene-centric* classifications of individuals, allowing for dependencies between omics layers (DEST*in*CT WP1,2; 2-DEST*in*CT WP1,3) and its application (once available) has been integrated in recent clinical oriented project proposals for pancreas cancer (e.g., TÉLÉVIE, analytics and data collection coordinated by the PI). Furthermore, as for rare disease samples sizes may be small, extra power can be gained by well-conducted meta-analyses (DEST*in*CT WP3).

3. Precision medicine

Administering the most optimal treatment for an individual patient, assumes having tested a treatment selection scheme first in animal models and second on a limited number of patients, prior to having tested the approach via appropriate clinical trials for precision medicine. The latter assumes specifying patient trial entry criteria and thus an accurate definition of the phenotype. Here is where trait heterogeneity comes into play (2-DEST*in*CT) and the expansion of samples sizes to enable the assessment of general population structure (DEST*in*cT WP1), to ultimately obtain disease-specific (molecular) subclasses of individuals, allowing for epistatic differences.