Determining the state of the art for identifying the gene being targeted by a non-coding, disease associated SNP

# Introduction

In our manuscript we consider DEPICT to be the current state-of-the-art.

Here we explain why DEPICT was selected over other methods.

# Background

For an overview of the available methods, we use the table as provided by Watanabe et al.

Table

Description automatically generated with medium confidence

From the “Gene-based test/Gene-set analyses”, and based on the column “Map SNPs to genes”, there are seven methods available (VEGAS, MAGMA, Pascal, MAGENTA, INRICH, DEPICT, and FUMA). Because MAGMA was developed by the same research group as FUMA, we consider it to be its predecessor.

For the state-of-the-art, we consider three criteria:

* The method must be (somewhat) recent
* The method must be commonly used, as indicated by its citations
* The method must achieve a high performance (preferably the best)

# Recency and usage frequency

To determine how recent a tool is, and how frequently a tool has been used, we look at the number of times its descriptive article has been cited on Pubmed, searching for the article cited in the study by Watanabe et al. (search date 8-5-2022).

|  |  |  |
| --- | --- | --- |
| **Method** | **Publication year** | **Number of times cited in Pubmed on 8-5-2022** |
| VEGAS | 2015 | 140 |
| MAGMA | 2015 | 756 |
| Pascal | 2016 | 143 |
| MAGENTA | 2010 | 283 |
| INRICH | 2012 | 146 |
| DEPICT | 2015 | 347 |
| FUMA | 2017 | 725 |

Based on the table above, DEPICT and FUMA are selected for further testing. Reasons for excluding the other methods are listed in the table below.

|  |  |
| --- | --- |
| **Method** | **Reason for exclusion** |
| VEGAS | Relatively little used |
| MAGMA | Has been superseded by FUMA |
| Pascal | Relatively little used |
| MAGENTA | Too old |
| INRICH | Relatively little used |

# Comparing performance of DEPICT and FUMA

We test our four reference sets on both DEPICT and the SNP2Gene function of FUMA. We test two variations of FUMA: The first is its default settings as set on https://fuma.ctglab.nl/, for the second variation we enable the eQTL mapping and 3D Chromatin Interaction mapping, both with all tissue type datasets as described in the manuscript. Gene candidates for SNPs are ranked, based upon which the ROC-AUC, Recall in the top-1, and Recall in the top-3 are calculated as described in the manuscript.

The results are shown below.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Method** | **Reference set** | **Number of SNPs** | **Total number of positive cases** | **ROC-AUC** | **Recall in top-1** | **Recall in top-3** |
| FUMA default | Teslovich | 72 | 74 | 75.4 | 41 | 64 |
| FUMA default | DeRycke | 54 | 66 | 66.2 | 32 | 60 |
| FUMA default | Farashi full | 62 | 62 | 58.2 | 29 | 56 |
| FUMA default | Farashi p-value cutoff | 55 | 55 | 59.8 | 27 | 49 |
| FUMA extended | Teslovich | 84 | 97 | 49.2 | 7 | 27 |
| FUMA extended | DeRycke | 74 | 145 | 50.9 | 8 | 26 |
| FUMA extended | Farashi full | 48 | 52 | 52.1 | 5 | 10 |
| FUMA extended | Farashi p-value cutoff | 37 | 39 | 52.2 | 3 | 8 |
| DEPICT | Teslovich | 70 | 71 | 86.2 | 55 | 66 |
| DEPICT | DeRycke | 45 | 49 | 79.5 | 31 | 44 |
| DEPICT | Farashi full | 97 | 97 | 76.7 | 62 | 88 |
| DEPICT | Farashi p-value cutoff | 46 | 46 | 75.9 | 30 | 31 |

For the FUMA default, the mean AUC across all four reference sets is 64.9% (min-max: 58.2-75.4), while for FUMA extended the mean AUC is 51.1% (min-max: 49.2-52.2). For DEPICT the mean AUC is 79.6% (min-max: 75.9-86.2).

For the Teslovich and DeRycke reference sets, FUMA covers more SNPs than DEPICT, although FUMA covers the full Farashi reference set rather poorly. FUMA extended covers more genes and SNPs, but based on its AUC its ranking performance is worse than FUMA default.

# Direct comparison FUMA to DEPICT

To directly compare ranking performance between FUMA and DEPICT, we select the intersection between their outputs and calculate the performance metrics.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Method** | **Reference set** | **Number of SNPs** | **Total number of positive cases** | **ROC-AUC** | **Recall in top-1** | **Recall in top-3** |
| FUMA  default | Teslovich | 61 | 62 | 75.2 | 39 | 57 |
| DEPICT | Teslovich | 61 | 62 | 85.5 | 48 | 57 |
| FUMA  default | DeRycke | 41 | 43 | 79.3 | 31 | 41 |
| DEPICT | DeRycke | 41 | 43 | 81.4 | 31 | 40 |
| FUMA  default | Farashi full | 48 | 48 | 73.7 | 32 | 44 |
| DEPICT | Farashi full | 48 | 48 | 71.6 | 28 | 43 |
| FUMA default | Farashi p-value cutoff | 43 | 43 | 72.2 | 28 | 39 |
| DEPICT | Farashi p-value cutoff | 43 | 43 | 71.3 | 25 | 39 |
| FUMA  extended | Teslovich | 67 | 75 | 76.1 | 43 | 67 |
| DEPICT (FUMA extended) | Teslovich | 67 | 75 | 85.7 | 52 | 70 |
| FUMA  extended | DeRycke | 45 | 58 | 74.4 | 30 | 50 |
| DEPICT  (FUMA extended) | DeRycke | 45 | 58 | 79.9 | 31 | 50 |
| FUMA  extended | Farashi full | 30 | 31 | 65.9 | 16 | 27 |
| DEPICT (FUMA extended) | Farashi full | 30 | 31 | 57.7 | 13 | 25 |
| FUMA  extended | Farashi p-value cutoff | 26 | 27 | 64.1 | 14 | 24 |
| DEPICT (FUMA extended) | Farashi p-value cutoff | 26 | 27 | 56.2 | 11 | 22 |

The mean AUC achieved by FUMA on the FUMA (default) – DEPICT intersection across all reference sets is 75.1 (min-max: 72.2 – 79.3), while DEPICT achieved a mean AUC of 77.5 (min-max: 71.3-85.5) on the same set. For the FUMA (extended) – DEPICT intersection the mean AUC achieved by FUMA is 70.1% (min-max: 64.1-76.1), while for DEPICT this was 69.9% (min-max: 56.2-85.7).

# Discussion

FUMA only achieves a higher AUC than DEPICT on the intersection of the FUMA (extended) and DEPICT set, by 0.2 percentage points. In all other experiments, DEPICT achieves a higher AUC, by higher margins. Although FUMA (extended) covers more SNPs and genes from the reference sets, it achieves the lowest AUC across all reference sets. Therefore, based upon these results, we identify DEPICT as the current state of the art.

More recently, the OpenTargets dataset has become available. Future work may also want to perform similar experiments as described above on their results.