

# An integrated interactive ecosystem for alkaptonuria: a tool for physicians and researchers

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## Summary

In this work, it has been developed an Alkaptonuria (AKU)-dedicated database, ApreciseKURE, which is an effective tool for registered researchers, clinicians and patients who could both easily access all the current information, as well as being able to insert new data, refreshing or replacing previous entries. Data are divided into different sections: genetic, protein, biochemical, histopathologic and clinical (Fig. 2). An algorithm was developed to analyze data and build up a refreshable correlation matrix based on Pearson's correlation coefficient and P value. Together with the mathematical and statistical interpretation, a biological explanation of the results is needed in order to investigate on AKU biomarkers. This dynamic tool could be useful for biomarkers investigation also in other osteoarticular diseases and it is a good starting point for the creation of data management and analysis model appropriate for Precision Medicine (PM).

## Description

**Introduction:** Alkaptonuria (AKU) is a rare and genetic disease that causes discoloration of bone and cartilage ('ochronosis') and induces early-onset osteoarthritis. AKU data have not been organized yet and the disease has no approved biomarkers. The ability to collect, integrate and analyze relevant data streams is the core for developing an AKU-dedicated "Precision Medicine Ecosystem" where biological resources are shared between researchers, clinicians and patients. Computational modelling can be a useful guide to generate an exhaustive and dynamic picture of the individual and to identify the molecular interactions between biomarkers on which progressive diseases are based.

**Methods:** It has been built a new integrated interactive database thanks to MySQL. In addition, data are statistically analyzed by R software ([www.r-project.org](http://www.r-project.org)) based on Pearson's correlation coefficient and *p*-value.

**Results:** Data regarding AKU affected patients have been acquired and analyzed. In order to make them suitable for research, they are electronically organized in an interactive and searchable database thanks to MySQL (Fig.1).

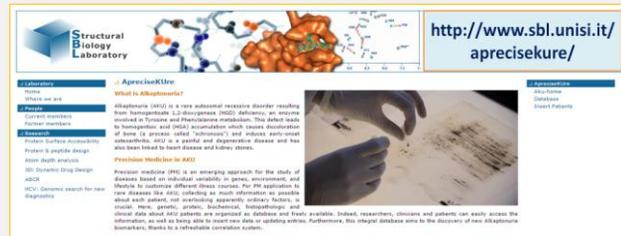


Fig 1. ApreciseKURE Database Homepage

The database is an effective tool in order to access to all the current information and to insert or update new data (Spiga O. et al, 2017) paving the way for an AKU-dedicated PME creation. Moreover, it has been developed an algorithm to build up a

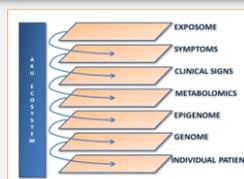


Fig 2. Biomarkers stratification

refreshable correlation matrix based on Pearson's correlation coefficient and *p*-value. A correlation matrix is a table containing the correlation coefficients between each variable and is used to examine the dependence between multiple variables at the same time (Fig.3). By visualizing every pair of variables, a complete statistical analysis can be obtained. This system gives a general picture of variable associations and its refresh feature allows the monitoring of renewable relationships between the most recent data inserted in the database; this is a crucial point for a chronic and non-lethal disease like AKU and for a personalized knowledge of affected population.

	age	sex	chitotriosidase	serum_hga	crp	crp_elisa	mmp3	scpp	PSH	CysSP	CyglySP
PTI	<b>0.327</b>	0.197	0.273	0.021	0.228	0.262	0.016	0.012	<b>-0.452</b>	<b>0.896</b>	<b>0.563</b>
AKUSS_jointpain	0.244	-0.05	0.212	-0.046	0.053	0.086	-0.006	0.01	-0.087	0.073	0.018
AKUSS_spinalpain	0.258	-0.063	0.177	0.012	0.067	0.118	-0.011	0.007	-0.139	0.193	0.076
KOOSpain	<b>-0.361</b>	-0.092	-0.276	-0.005	-0.113	-0.131	-0.084	0.031	0.163	-0.101	-0.024
KOOSymptoms	<b>-0.357</b>	-0.137	-0.226	0.025	-0.167	-0.151	-0.005	0.041	0.203	-0.159	-0.086
KOOSdaily_living	<b>-0.386</b>	-0.122	-0.253	0.006	-0.085	-0.075	-0.04	0.025	0.168	-0.118	-0.027
KOOSport	<b>-0.413</b>	-0.092	<b>-0.301</b>	-0.035	-0.067	-0.122	-0.081	0.011	0.248	-0.185	-0.062

Fig 3. Correlation matrix in ApreciseKURE Database Homepage

We invite users of the ApreciseKURE database not to look at the Pearson's index only as the numeric value, but to focus also on a deeper understanding of possible biological significance of the compared markers. This approach can lead into discovery of interesting correlations between biomarkers not considered before and to point out eventual AKU critical points. For example, our analysis indicates an inverse statistic correlation between *Cystatin C (CysC)* and *Cathepsin D (CatD)* (Pearson's index -0.32 and *p*-value 0.0470). It has suggested that *CysC* is not an appropriate marker for kidney dysfunction in AKU because its levels could be modified by *CatD* action which is responsible for *CysC* degradation (Lenarčič B. et al, 1991). *CatD* levels are particularly high in arthritic diseases thus, *CysC* levels could be unreliable and not suitable for monitoring kidney function in AKU and in other common arthritic diseases.

**Conclusion:** This dynamic tool could be useful for biomarkers investigation also in other osteoarticular diseases and it is a good starting point for the creation of data management and analysis model appropriate for PM. With our database and this innovative analytic approach, it has been possible to become aware of the failure of biomarkers clinically used and to improve the detection of more exploitable prognostic biomarkers for a more reliable AKU patients clinical monitoring.

## References

- R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: <http://www.R-project.org>.
- Spiga O et al. ApreciseKURE: an approach of Precision Medicine in a Rare Disease. *BMC Medical Informatics and Decision Making*. 2017; 17:42.
- Lenarčič B et al. Inactivation of human cystatin C and kininogen by human cathepsin D. *FEBS Lett*. 1991;280(2):211-5.