Tool	iMRMC: Software to do multi-reader multi-case statistical analysis of reader studies
Technical Description	The primary objective of the iMRMC statistical software is to assist investigators with analyzing and sizing multi-reader multi-case (MRMC) reader studies that compare the difference in the area under Receiver Operating Characteristic curves (AUCs) from two modalities. The iMRMC application is a software package that includes simulation tools to characterize bias and variance of the MRMC variance estimates. The core elements of this application include the ability to perform MRMC variance analysis and the ability to size an MRMC trial. • The core iMRMC application is a stand-alone, precompiled, license-free Java applications and the source code. It can be used in GUI mode or on the command line. • There is also an R package that utilizes the core Java application. Examples for using the programs can be found in the R help files. The software treats arbitrary study designs that are not "fully-crossed"
Intended Purpose	The iMRMC package analyzes data from MRMC studies. MRMC stands for Multiple Readers and Multiple Cases (MRMC). MRMC studies are often imaging studies where clinicians (readers) evaluate patient images (cases). The MRMC methods apply to any scenario in which clinicians interpret data to make decisions. The iMRMC package calculates the reader-averaged area under the receiver operating characteristic curve: the AUC of the ROC curve. AUC is a diagnostic performance measure. Additional functions analyze other endpoints (binary performance and score differences). This package also estimates variances, confidence intervals and p-values. These uncertainty characteristics are needed for hypothesis tests to size and assess the efficacy of diagnostic imaging devices and computer aids (artificial intelligence). Why is this analysis important? ... Many imaging studies are designed so that every reader reads every case in all modalities, a fully-crossed study. In this case, the data is cross-correlated, and we consider the readers and cases to be cross-correlated random effects. An MRMC analysis accounts for the variability and correlations from the readers and cases when estimating variances, confidence intervals, and p-values. The functions in this package can treat arbitrary study designs and studies with missing data, not just fully-crossed study designs. The methods in the iMRMC package are not standard. The package permits industry statisticians to use a validated statistical analysis method without having to develop and validate it themselves.
Testing	The tool has been characterized through simulations (bias and variance of the estimates) and has been compared to other methods as appropriate for the task. Please cite one of these when you use the iMRMC software. • Gallas, B. D., Chen, W., Cole, E., Ochs, R., Petrick, N., Pisano, E. D., Sahiner, B., Samuelson, F. W., & Myers, K. J. (2019). Impact of prevalence and case distribution in lab-based diagnostic imaging studies. *Journal of Medical Imaging*, *6*(1), 015501. https://doi.org/10.1117/1.JMI.6.1.015501

	- o Desc: Study that uses the software and related research methods and study designs in a large study. Supplementary materials include data and scripts to reproduce study results. - Gallas, B. D. (2006). One-shot estimate of MRMC variance: AUC. *Acad Radiol*, *13*(3), 353–362. https://doi.org/10.1016/j.acra.2005.11.030 - o Desc: Original description of method and validation with simulations. Results comparable to jacknife resampling technique. - Gallas, B. D., Pennello, G. A., & Myers, K. J. (2007). Multireader multicase variance analysis for binary data. *Journal of the Optical Society of America. A, Optics, Image Science, and Vision*, *24*(12), B70-80. https://doi.org/10.1364/josaa.24.000b70 - o Generalize method to binary performance measures. - Gallas, B. D., Bandos, A., Samuelson, F., & Wagner, R. F. (2009). A framework for random-effects ROC analysis: Biases with the bootstrap and other variance estimators. *Commun Stat A-Theory*, *38*(15), 2586–2603. https://doi.org/10.1080/03610920802610084 - o Provide framework for understanding method and comparing to other methods analytically and with simulations. - Gallas, B. D., & Brown, D. G. (2008). Reader studies for validation of CAD systems. *Neural Networks Special Conference Issue*, *21*(2), 387–397. https://doi.org/10.1016/j.neunet.2007.12.013 - o Desc: Generalize method to treat arbitrary study designs.
Limitations	Currently, the tool can produce negative variance estimates. This happens for studies where the dataset is small.
Table of Contents/ Supporting Documentation	Tool websites: - Primary: https://github.com/DIDSR/iMRMC - Secondary: https://cran.r-project.org/web/packages/iMRMC/index.html User manual for java app - http://didsr.github.io/iMRMC/000_iMRMC/userManualPDF/iMRMCuserManual.pdf User manual for R package - https://cran.r-project.org/web/packages/iMRMC/iMRMC.pdf FAQs - https://github.com/DIDSR/iMRMC/wiki/iMRMC-FAQ Supplementary materials - Data and scripts to reproduce results for manuscripts that use iMRMC - https://github.com/DIDSR/iMRMC/wiki/iMRMC-Datasets **Related FDA Product Codes** (This is not a comprehensive list) - KPS: System, Tomography, Computed, Emission

- LLZ: System, Image Processing, Radiological
- PAA: Automated Breast Ultrasound
- POK: Computer-Assisted Diagnostic Software For Lesions Suspicious For Cancer
- QDQ: Radiological Computer Assisted Detection/Diagnosis Software For Lesions Suspicious For Cancer
- QPN: Software Algorithm Device To Assist Users In Digital Pathology

Related Work

- Chen, W., Gong, Q., Gallas, B.D. (2018). Paired split-plot designs of multireader multicase studies. Journal of Medical Imaging 5, 031410. https://doi.org/10.1117/1.JMI.5.3.031410
- Obuchowski, N.A., Gallas, B.D., Hillis, S.L. (2012). Multi-Reader ROC studies with Split-Plot Designs: A Comparison of Statistical Methods. Acad Radiol 19, 1508–1517. https://doi.org/10.1016/j.acra.2012.09.012
- Gallas, B.D., Chan, H.-P., D'Orsi, C.J., Dodd, L.E., Giger, M.L., Gur, D., Krupinski, E.A., Metz, C.E., Myers, K.J., Obuchowski, N.A., Sahiner, B., Toledano, A.Y., Zuley, M.L. (2012). Evaluating imaging and computer-aided detection and diagnosis devices at the FDA. Acad Radiol 19, 463–477. https://doi.org/10.1016/j.acra.2011.12.016
- Obuchowski, N. A., Gallas, B. D., & Hillis, S. L. (2012). Multi-Reader ROC studies with Split-Plot Designs: A Comparison of Statistical Methods. *Academic Radiology*, *19*(12), 1508–1517. https://doi.org/10.1016/j.acra.2012.09.012
- Gallas, B. D., & Hillis, S. L. (2014). Generalized Roe and Metz ROC model: Analytic link between simulated decision scores and empirical AUC variances and covariances. *J Med Img*, *1*(3), 031006. https://doi.org/doi:10.1117/1.JMI.1.3.031006

Current research

- LINK to High-Throughput Truthing (HTT) project: The goal of the High-Throughput Truthing (HTT) project is to produce a **validation dataset** established by pathologist annotations for artificial intelligence algorithms analyzing digital scans of pathology slides: data (images + annotations). We are pursuing the qualification of the final validation dataset as an FDA-qualified medical device development tool MDDT to become a high-value public resource that can be used in AI/ML algorithm submissions and guide others to develop quality validation datasets.

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