39P Clinical Relevance of Alterations in Cancer (CRAC): a knowledge base for selecting biomarkers for molecularly matched therapy in cancer patients

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MAP 2022
14-16 October 2022
Amsterdam, Netherlands

Background

Multigene genomic testing via NGS can detect multiple genomic alterations. To rank the associations of these findings and their association with therapy, levels of evidence (LOE) are used. The use of LOE requires both understanding the functional consequences of the genomic alterations and an extensive literature search. These and have less practical value for narrowing down therapy recommendations in cases when multiple genomic alterations with the same LOE are found. Efficient tools to solve this problems are in demand.

Methods

- For each type of genomic alteration, depending on the gene and tumor type, a score from 1 to 10 was assigned independently by a group of biologists and oncologists; average scores were used for the CRAC database.
- Scores reflected the theoretical estimation of percentage of patients harboring specific biomarker that could be matched with relevant targeted therapy; the efficacy of therapy based on expected benefit; quality of data; expert opinion; potential obstacles associated with access to therapy (e.g., drug approvals, indications for use, status of relevant clinical trials, etc.).
- To test the utility of the database, we analyzed real-world comprehensive molecular profiling results (150+ gene NGS panels) (CMPR).
- Each genomic alteration was ranked using ESCAT. Additionally, each alteration was assigned a CRAC-score.

Results

- A total of 134 genes were selected for 16 malignancies with 2 genomic alterations for each in average, with a total of 234 genomic alterations.
- Genomic alterations with CRAC-scores of 2-3 outnumbered alterations with CRAC-scores of 9-10 (36 vs 2%).
- The majority (17 vs 13%) of genes irrespective of alteration type had average scores of 2-2.5, 3.5-4, within one tumor type. To test the practical value and applicability of CRAC-scores in clinical setting, 208 reports gathered following comprehensive molecular profiling of the tumor (23.5% CRC, 16.3% PAAD, 11% BRCA, 49% - other) with a total of 210 genomic alterations were analyzed.
- 64 (31%) reports contained 79 genomic alterations of I-III ESCAT LOE, 114 (55%) – 131 genomic alterations that could be assigned IV ESCAT LOE.
- The highest CRAC-scores reflected the highest LOE of alteration-drug pair.
- No genomic alteration–drug pair with the same LOE had the same CRAC-score. ESCAT LOE IIIA and IV alterations and had the largest range of CRAC-scores (2-10 and 1-9, respectively).
- CRAC made it possible to identify additional potentially targetable genomic alterations with CRAC-scores 2-4. Noteworthy, 45% of these were not present in the original tumor molecular profiling reports.
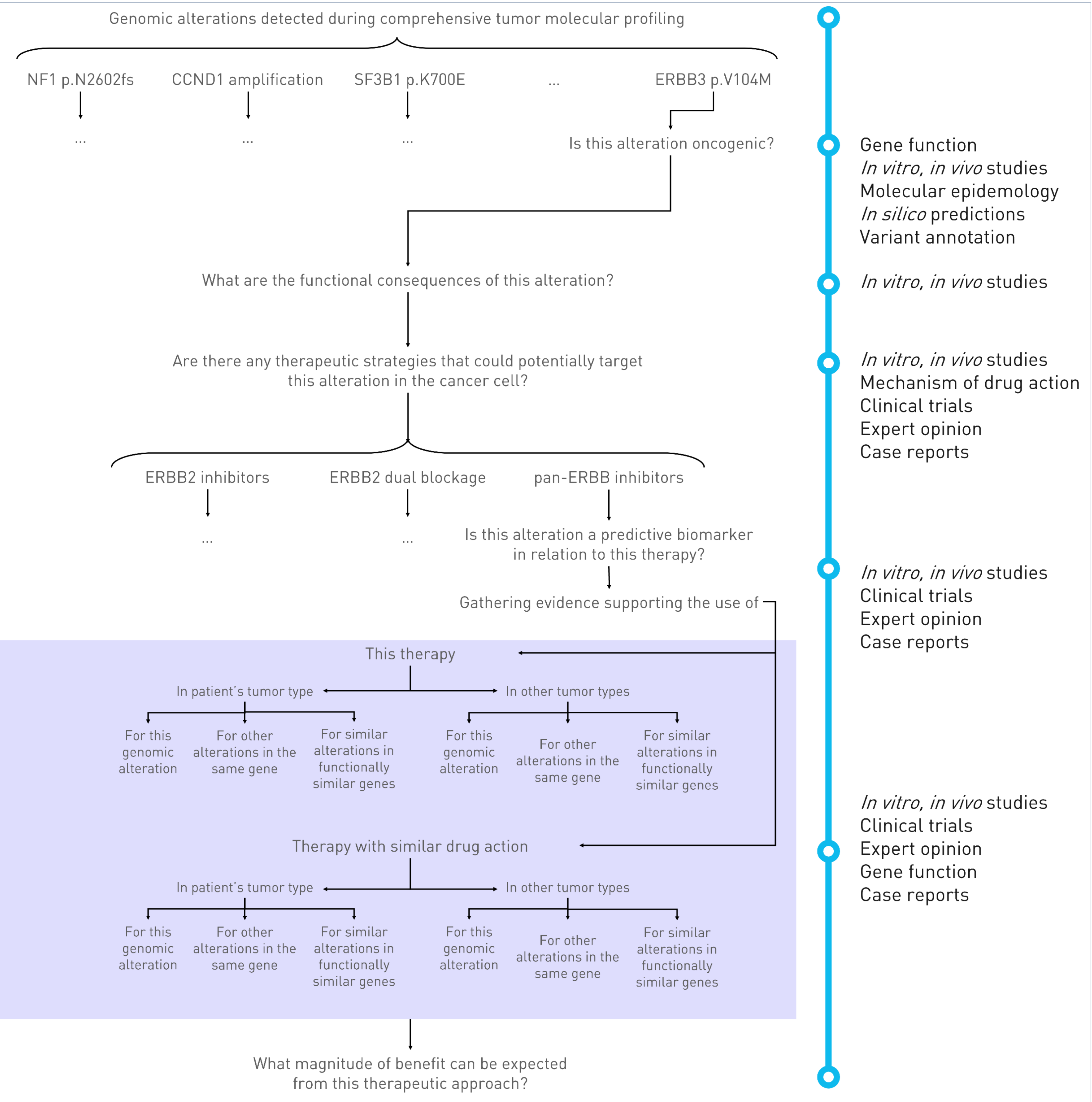
Fig.1 Schematic representation of steps required for accurate interpretation of the CMPR results. This process is time-consuming and requires expertise in both molecular biology and clinical oncology.
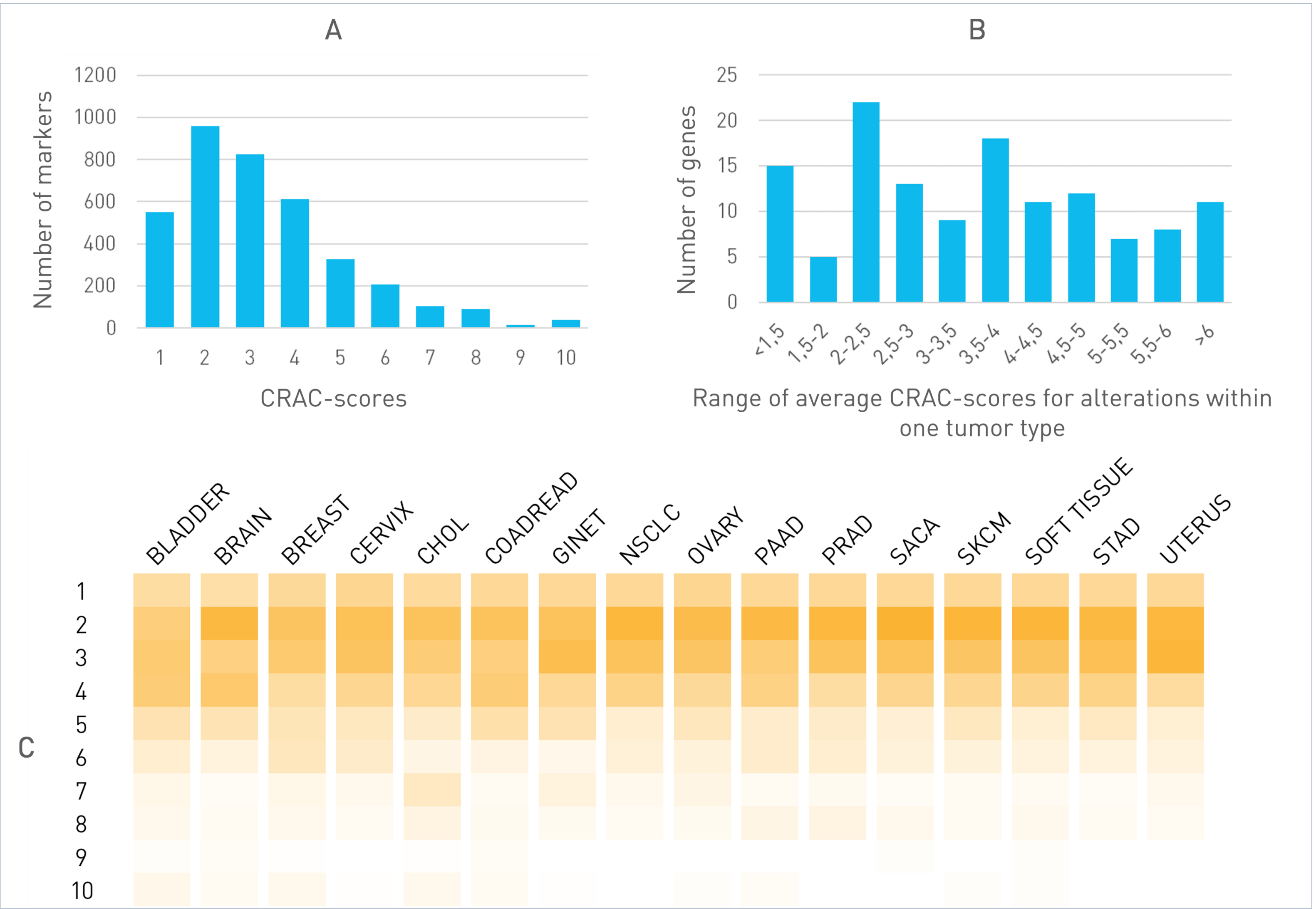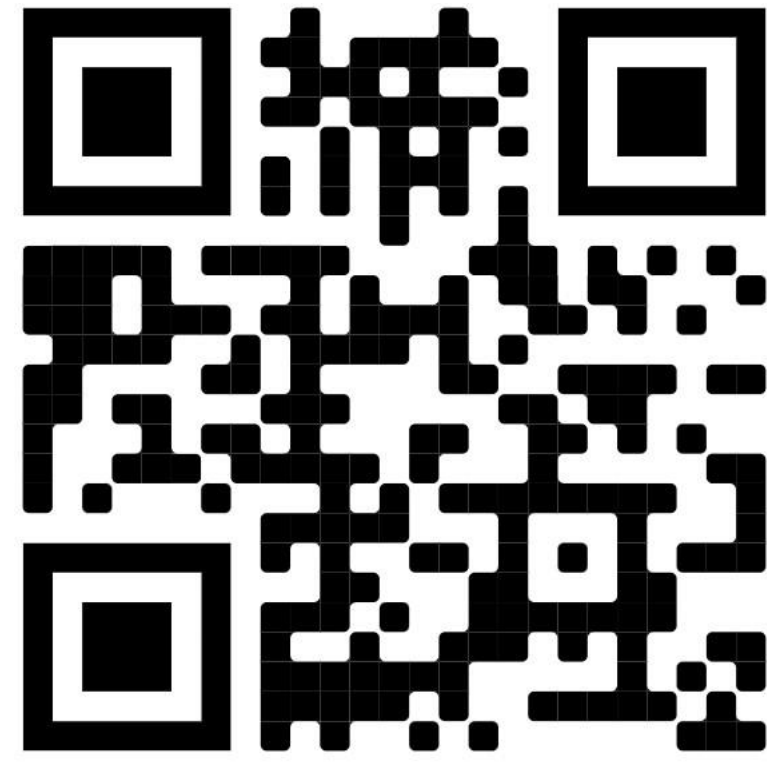

Fig.2 Description of the information contained in the CRAC database. **(A)** Distribution of the number of biomarkers in the database by CRAC-scores; **(B)** Distribution of the number of genes contained in the database by average CRAC-scores among tumor types; **(C)** Distribution of CRAC-scores by tumor type in the database
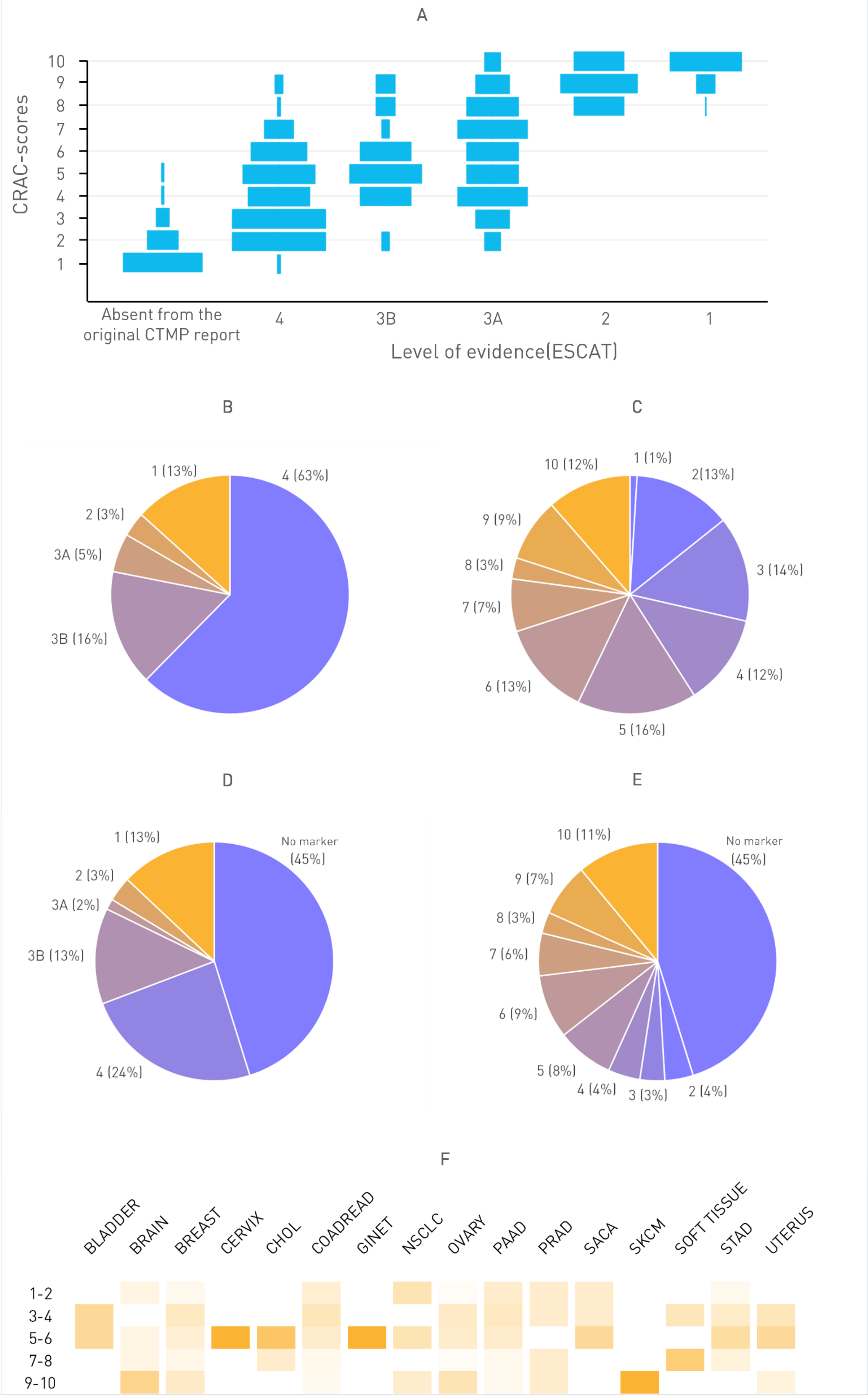
Fig.3 Utility of the ESCAT and CRAC to characterize biomarkers found in 208 patients following CMPR. **(A)** Distribution of CRAC-scores for markers of various ESCAT LOE. Some of these were not present in the original CMPR reports; **(B)** Distribution of ESCAT LOE among all biomarkers (N=210) found in the study population; **(C)** Distribution of CRAC-scores among all (N=305) biomarkers found in the study population; **(D)** Occurrence of biomarkers among all patients and the corresponding LOE (if more than one biomarker was found in one patient, only the biomarker with the highest LOE was taken into account); **(E)** The occurrence of biomarkers among all patients and the corresponding CRAC-scores (if more than one biomarker was found in one patient, only the biomarker with the highest CRAC-score was taken into account); **(F)** Distribution of CRAC-scores of the detected biomarkers in the study population for various tumor types.

Conclusions

- Using CRAC-scores to identify clinically significant potentially targetable genomic alterations proved to be a more comprehensive approach compared to designating ESCAT LOE (each LOE was represented by ⩾3 scores; each CMPR report had biomarkers with ⩾2 scores).
- CRAC available at crac.oncoatlas.ru.

Try CRAC for your patients!

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