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— *with international search report (Art. 21(3))*

[Continued on next page]

(54) Title: MOLECULAR PROFILING FOR CANCER

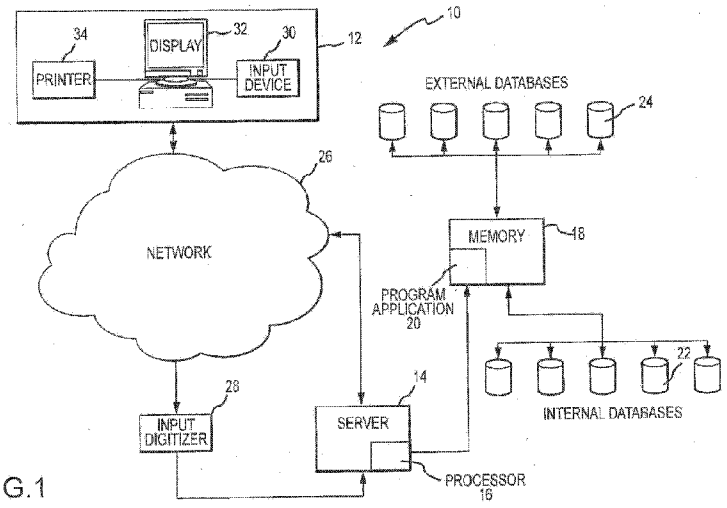

FIG.1

(57) Abstract: Provided herein are methods and systems of molecular profiling of diseases, such as cancer. In some embodiments, the molecular profiling can be used to identify treatments that have likely benefit for a cancer, such as treatments that were not initially identified as a treatment for the disease or not expected to be a treatment for a particular disease. The molecular profiling can be used to identify likely have lack of benefit for treating the cancer.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/073184

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 33/53 (2014.01)
USPC - 435/6.13
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C12Q 1/68; C40B 30/00; G01N 33/53, 33/574; G06F 19/10, 19/24 (2014.01)
USPC - 435/6.13, 6.14, 7.23; 506/17, 18; 702/19

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - C12Q 1/6886, 2600/118; G01N 33/53, 33/574, 2800/52, 2800/54, 2800/56 (2014.02)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase, Google Patents, Google, Pubmed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/092336 A2 (ALARCON et al) 05 July 2012 (05.07.2012) entire document	1, 2, 4, 6, 18, 19, 21, 23, 91, 103, 104
A	US 2010/0144836 A1 (VAN ENGELAND et al) 10 June 2010 (10.06.2010) entire document	1, 2, 4, 6, 18, 19, 21, 23, 91, 103, 104
A	WO 2003/082072 A2 (HARBECK et al) 09 October 2003 (09.10.2003) entire document	1, 2, 4, 6, 18, 19, 21, 23, 91, 103, 104
A	WO 2010/123982 A2 (GODWIN et al) 28 October 2010 (28.10.2010) entire document	1, 2, 4, 6, 18, 19, 21, 23, 91, 103, 104
P,X	WO 2012/170715 A1 (DANENBERG et al) 13 December 2012 (13.12.2012) entire document	1, 2, 4, 6, 18, 19, 21, 23, 91, 103, 104
T,X	US 2014/0018254 A1 (VON HOFF et al) 16 January 2014 (16.01.2014) entire document	1, 2, 4, 6, 18, 19, 21, 23, 91, 103, 104

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 June 2014	23 JUN 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/073184

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8-17,25, 33, 41, 42, 50, 51, 59, 67, 68, 82, 90, 92, 100-102, 105-160
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheets.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2, 4, 6, 18, 19, 21, 23, 91, 103, and 104, limited to ovarian cancer and the panel of gene or gene products selected to be TLE3, TUBB3, PGP, SPARCm (mono), and SPARCp (poly) and the rules corresponding to that panel selection.

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-7, 18-24, 26-32, 34-40, 43-49, 52-58, 60-66, 69-81, 83-89, 91, 93-99, 103, and 104 are drawn to methods of identifying one or more candidate treatment for a cancer in a subject in need thereof.

The first invention of Group I+ is restricted to methods of identifying one or more candidate treatment or candidate clinical trial for a subject having a cancer, comprising: (a) determining a molecular profile for a sample from the subject by assessing a panel of gene or gene products; and (b) identifying one or more treatment that is beneficially associated with the molecular profile of the subject according to the determining in (a) and one or more rules, thereby identifying the one or more candidate treatment; wherein the cancer is selected to be ovarian cancer, wherein the panel of gene or gene products is selected to be TLE3, TUBB3, PGP, SPARCm (mono), and SPARCp (poly) corresponding to the first line entries of Table 21 and Table 7; wherein the one or more rules is selected to be those corresponding to "Taxanes" entry (Table 22, Pg. 178 and Table 8, Pg. 128) and the gene panel selection of TLE3, TUBB3, PGP, SPARCm (mono), and SPARCp (poly). It is believed that claims 1, 2, 4, 6, 18, 19, 21, 23, 91, 103, and 104 read on this first named invention and thus these claims will be searched without fee to the extent that they read on ovarian cancer and the panel of gene or gene products selected to be TLE3, TUBB3, PGP, SPARCm (mono), and SPARCp (poly) and the rules corresponding to that panel selection.

Applicant is invited to elect additional types of cancers and/or panels of gene or gene products and/or rules for each method to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be methods of identifying one or more candidate treatment or candidate clinical trial for a subject having a cancer, comprising: (a) determining a molecular profile for a sample from the subject by assessing a panel of gene or gene products; and (b) identifying one or more treatment that is beneficially associated with the molecular profile of the subject according to the determining in (a) and one or more rules, thereby identifying the one or more candidate treatment; wherein the cancer is selected to be ovarian cancer, wherein the panel of gene or gene products is selected to be TOPO1; wherein the one or more rules is selected to be those corresponding to "TOPO1 inhibitors" entry and the gene panel selection of TOPO1. Additional types of cancers and/or panels of gene or gene products and/or rules will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulas do not share a significant structural element, requiring the selection of alternatives for the type of cancer "the cancer comprises a prostate, bladder, kidney, lung, breast, or liver cancer"; panel of gene or gene products "the panel of gene or gene products comprises ABL1, AKT1, ALK, APC, AR, ATM, BRAF, CDH1, cKIT, cMET, CSF1R, CTNNB1, EGFR, ER, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, FLT3, GNA11, GNAQ, GNAS, HER2, HNF1A, HRAS, IDH1, JAK2, JAK3, KDR (VEGFR2), KRAS, MGMT, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PGP, PIK3CA, PR, PTEN, PTPN11, RB1, RET, RRM1, SMAD4, SMARCB1, SMO, SPARC, STK11, TLE3, TOP2A, TOPO1, TP53, TS, TUBB3 and VHL"; and rules "one or more rules in Table 25 or any of Tables 7-22".

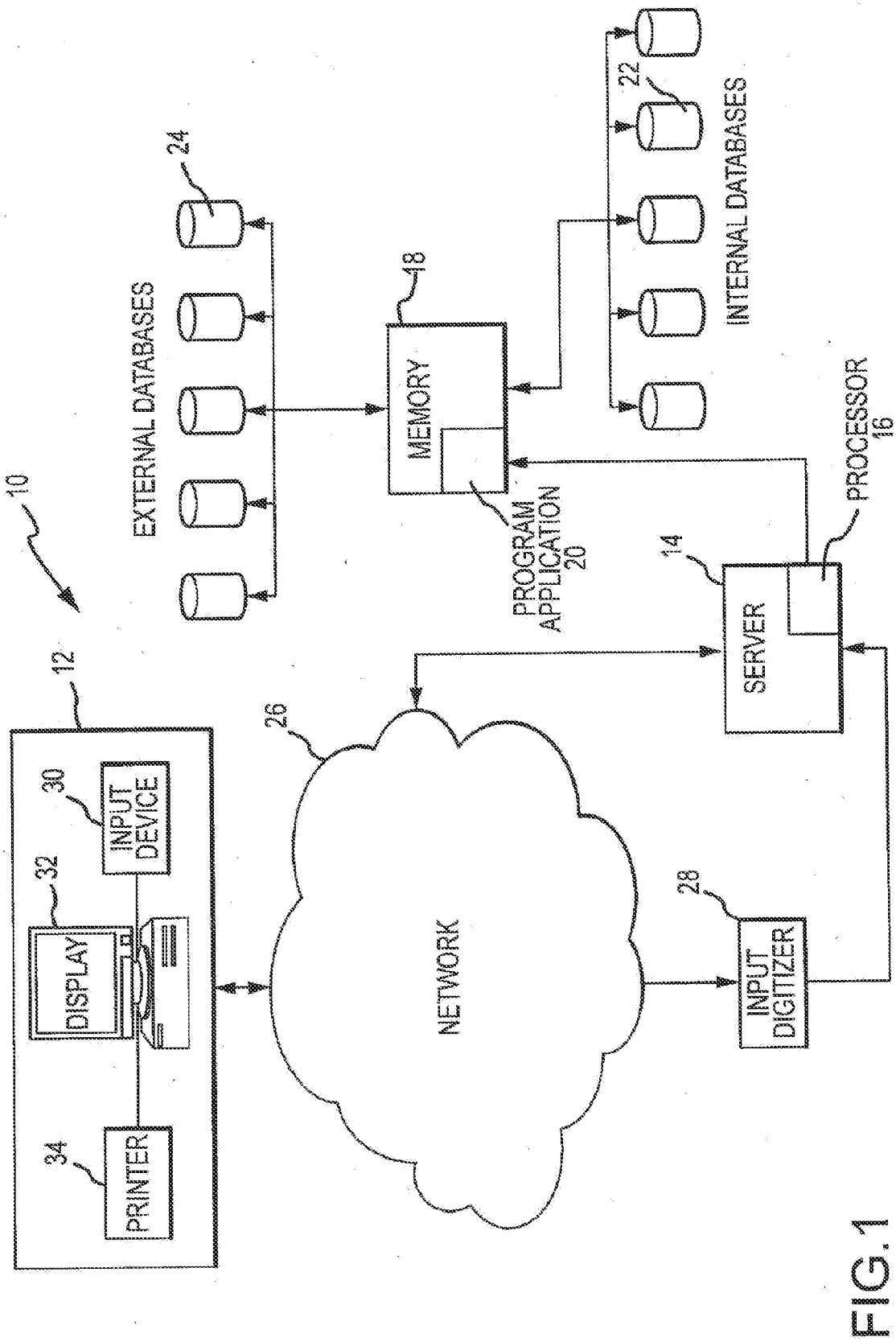
The Groups I+ share the technical features of a method of identifying one or more candidate treatment for a cancer in a subject in need thereof; a method of identifying one or more candidate treatment for an ovarian cancer in a subject in need thereof; a method of identifying one or more candidate treatment for a breast cancer in a subject in need thereof; a method of identifying one or more candidate treatment for a skin cancer (melanoma) in a subject in need thereof; a method of identifying one or more candidate treatment for a uveal melanoma cancer in a subject in need thereof; a method of identifying one or more candidate treatment for a colorectal cancer in a subject in need thereof; a method of identifying one or more candidate treatment for a lung cancer in a subject in need thereof; a method of identifying one or more candidate treatment for a glioma brain cancer in a subject in need thereof; a method of identifying one or more candidate treatment for a gastrointestinal stromal tumor (GIST) cancer in a subject in need thereof; a method of identifying one or more candidate treatment for a prostate cancer in a subject in need thereof; and a method of identifying one or more candidate clinical trial for a subject having a cancer; said methods comprising: (a) determining a molecular profile for a sample from the subject by assessing a panel of gene or gene products; and (b) identifying one or more treatment that is beneficially associated with the molecular profile of the subject, and optionally one or more treatment associated with lack of benefit, according to the determining in (a) and one or more rules, thereby identifying the one or more candidate treatment or the one or more candidate clinical trial. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2010/0144836 A1 to Van Engeland et al. discloses a method of identifying one or more candidate treatment for a cancer in a subject in need thereof (methods for determining suitable treatment regimens for cancer, Abstract; In this method, a sample is obtained from a subject suffering from, or suspected of suffering from any appropriate cancer in accordance with this invention, Para. [0190]); a method of identifying one or more candidate treatment for an ovarian cancer in a subject in need thereof (methods for determining suitable treatment regimens for cancer, Abstract; In this method, a sample is obtained from a subject suffering from, or suspected of suffering from any appropriate cancer in accordance with this invention, Para. [0190]; ovarian cancer, Para. [0079]); a method of identifying one or more candidate treatment for a breast cancer in a subject in need thereof (methods for determining suitable treatment regimens for cancer, Abstract; In this method, a sample is obtained from a subject suffering from, or suspected of suffering from any appropriate cancer in accordance with this invention, Para. [0190]; breast cancer, Para. [0079]); a method of identifying one or more candidate treatment for a skin cancer (melanoma) in a subject in need thereof (methods for determining suitable treatment regimens for cancer, Abstract; In this method, a sample is obtained from a subject suffering from, or suspected of suffering from any appropriate cancer in accordance with this invention, Para. [0190]; cancer types comprised melanoma, Para. [0371]); a method of identifying one or more candidate treatment for a colorectal cancer in a subject in need thereof (methods for determining suitable treatment regimens for cancer, Abstract; In this method, a sample is obtained from a subject suffering from, or suspected of suffering from any appropriate cancer in accordance with this invention, Para. [0190]; gastrointestinal cancers such as colorectal cancer, Para. [0024]); a method of identifying one or more candidate treatment for a lung cancer in a subject in need thereof (methods for determining suitable treatment regimens for cancer, Abstract; In this method, a sample is obtained from a subject suffering from, or suspected of suffering from any appropriate cancer in accordance with this invention, Para. [0190]; 21 lung and 22 bladder cancer samples, Para. [0435]); a method of identifying one or more candidate treatment for a glioma brain cancer in a subject in need thereof (methods for determining suitable treatment regimens for cancer, Abstract; In this method, a sample is obtained from a subject suffering from, or suspected of suffering from any appropriate cancer in accordance with this invention, Para. [0190]; brain cancer, Para. [0010]; glioblastoma, Para. [0011]); a method of identifying one or more candidate treatment for a prostate cancer in a subject in need thereof (methods for determining suitable treatment regimens for cancer, Abstract; In this method, a sample is obtained from a subject suffering from, or suspected of suffering from any appropriate cancer in accordance with this invention, Para. [0190]; prostate cancer, Para. [0079]); said methods comprising determining a molecular profile for a sample from the subject by assessing a panel of gene or gene products (levels of gene expression of at least one gene ...including panels ...are determined using reverse transcriptase polymerase chain reaction (RT-PCR), Para. [0093]; measured in order to determine if it is statistically significant in the sample, Para. [0088]; expression profiles, Para. [0488]); and identifying one or more treatment that is beneficially associated with the molecular profile of the subject according to the determining in and one or more rules, thereby identifying the one or more candidate treatment (pharmacogenetic methods for determining suitable treatment regimens for cancer and methods for treating cancer patients, based around selection of the patients according to the methods of the invention, Para. [0001]; protein expression of the at least one gene ...is observed in the sample in order ...to make a decision on the best course of treatment, Para. [0087]; selecting suitable treatment regimens and for determining the likelihood of successful treatment or resistance to treatment with certain anti-cancer agents, Para. [0170]).

Further, WO 2010/123982 A2 to Godwin et al. discloses a method of identifying one or more candidate treatment for a gastrointestinal stromal tumor (GIST) cancer in a subject in need thereof (methods are disclosed for identifying agents useful for the treatment of malignancy, particularly GISTs, Abstract), said method comprising determining a molecular profile for a sample from the subject by assessing a panel of gene or gene products (gene expression profile that could be predictive of likely IM induced cytoreduction in GIST patients prior to therapy, Pg. 33, Lns. 19-20; qRT-PCR assays are informative when adequate RNA samples can be obtained either from small needle biopsies or resected tumor samples, Pg. 34, Lns. 33-34); and identifying one or more treatment that is beneficially associated with the molecular profile of the subject according to the determining in and one or more rules, thereby identifying the one or more candidate treatment (gene expression profile that could be predictive of likely IM induced cytoreduction in GIST patients prior to therapy ....such a profile may be useful in determining appropriate personalized clinical treatment of GIST patients, Pg. 33, Lns. 19-23; demonstrated that expression of these ZNFs appeared to be coordinately regulated by IM treatment, Pg. 34, Lns. 6-7 and Fig. 3B).

Further still, WO 2003/082072 A2 to Harbeck et al. discloses a method of identifying one or more candidate treatment for a uveal melanoma cancer in a subject in need thereof (the present invention provides methods for determining treatment regimens for cancer subjects, Pg. 33, last partial paragraph; eye cancers such as but not limited to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma, Pg. 34, first partial paragraph), said method comprising determining a molecular profile for a sample from the subject by assessing a panel of gene or gene products (the methods of the present invention include measuring nucleic acid molecules that encode the uPA and PAI -1 proteins or their naturally occurring variants that are indicative of uPA and PAI-1 expression, Pg. 24, second full paragraph); and identifying one or more treatments that is beneficially associated with the molecular profile of the subject according to the determining in and one or more rules, thereby identifying the one or more candidate treatment (if the patient is classified as low risk, no further aggressive treatment regimen is provided; and if the patient is classified as high risk, an aggressive treatment regimen is provided. In a specific embodiment, the aggressive treatment comprises endocrine therapy and chemotherapy, Pg. 24, first partial paragraph; the level of uPA and the level ofPAI-1 or the levels of mRNA encoding uPA and PAI-1 in a patient are used to evaluate various treatment options, Pg. 26, fourth full paragraph).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.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INPUT DIGITIZER
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PROCESSOR 16
PROGRAM APPLICATION 20
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MEMORY
EXTERNAL DATABASES
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INTERNAL DATABASES
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FIG. 1