Adverse Drug Event Rate in Israeli Hospitals: Validation of an International Trigger Tool and an International Comparison Study

Eyal Zimlichman MD[1,7]*, Itai Gueta MD[2,7]*, Daniella Daliyot RN Msc[1], Amitai Ziv MD[1,7], Bernice Oberman Msc[3], Ohad Hochman MD[4,7], Ofer Tamir MD[5,7], Orna Tal MD[6,7] and Ronen Loebstein MD[1,7]

[1]Management, [2]Institute for Clinical Pharmacology and Toxicology and [3]Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Tel Hashomer, Israel
[4]Management, Hillel Yaffe Medical Center, Hadera, Israel
[5]Management, Padeh Poria Medical Center, Tiberias, Israel
[6]Management, Assaf Harofeh Medical Center, Zerifin, Israel
[7]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Adverse drug events (ADEs) are a major cause of morbidity and mortality worldwide. Hence, identifying and monitoring ADEs is of utmost importance. The Trigger Tool introduced by the Institute of Healthcare Improvement in the United States has been used in various countries worldwide, but has yet to be validated in Israel.

Objective: To validate the international Trigger Tool in Israel and to compare the results with those generated in various countries.

Methods: A retrospective descriptive correlative analysis surveying four general hospitals in Israel from different geographical regions was conducted. Patient medical charts (n=960) were screened for 17 established triggers and confirmed for the presence of an ADE. Trigger incidence was compared to the actual ADE rate. Further comparison among countries was conducted using published literature describing Trigger Tool validation in various countries.

Results: A total of 421 triggers in 279 hospitalizations were identified, of which 75 ADEs in 72 hospitalizations (7.5%) were confirmed. In addition, two ADEs were identified by chart review only. Mean positive predictive value was 17.81% and overall sensitivity was 97%. We found 1.54 ADEs for every 100 hospitalization days, 7.8 ADEs per 100 admissions, and 1.81 ADEs for every 1000 doses of medication. Of the 77 ADEs identified, 22.7% were defined as preventable.

Conclusions: Our results support the Trigger Tool validity in Israel as a standardized method. Further studies should evaluate between hospital and region differences in ADE rate, in particular for the preventable events.

IMAJ 2018; 20: 665–669

KEY WORDS: adverse drug events (ADE), in-hospital drug administration, Israeli hospital care, Trigger Tool

*The first and second authors contributed equally to this study

Adverse drug events (ADEs) are a major cause of morbidity and mortality worldwide. It is estimated that 1 out 5 in-hospital injuries or deaths are secondary to an ADE, with an annual prevalence of up to 450,000 injuries in the United States [1,2]. Medication errors have been shown to be responsible for 20% of ADEs, of which 28% were defined as preventable [3,4]. The latter is further accompanied by extra costs of more than US$3000 per patient with a 3 day increase in hospital stay [5]. In light of these findings, identifying and preventing ADEs when they do occur has been a cardinal role in ensuring patient safety and reducing healthcare costs [6].

The process of in-hospital drug administration is a multi-disciplinary process usually involving the treating physician, nursing staff, and pharmacists. This process is associated with an inherent potential for errors and hence, precise communication and highly efficient technologies are required for risk reduction. Among the technologies, computerized physician order entry (CPOE) systems and electronic medication-administration systems have been used to reduce prescription and transcription errors [7]. The former has been shown to reduce preventable ADEs by approximately one-third [8].

Aside from prevention, identifying an ADE is crucial for risk assessment and institutional reasoning. Monitoring patient files and voluntary staff reporting were demonstrated to be less thorough and more expensive [9]. In 2003, the Institute of Healthcare Improvement (IHI) in the United States presented the Trigger Tool for measuring ADEs [10]. The tool identifies potential ADEs by well-defined clues present in patient records, namely triggers. By using this tool, pre-defined triggers are screened within the patient's chart until they are found. This procedure is followed by tracking the trigger retrospectively, a process that might reveal an ADE. Its low cost and rapid training requirements enabled its introduction in many hospitals in the United States as well as in various European countries [11-18].

Furthermore, compared to other ADE reporting systems, the Trigger Tool was shown to assist in identifying 10 times more ADEs in approximately one-third of all hospitalizations. However, between-country differences in medical practices were shown to affect the Trigger Tool sensitivity and its positive predictive value (PPV). The latter has been reported to range between 4.0% and 21.5% in Britain and Belgium, respectively [16,17]. This finding is further reflected by variance in ADE prevalence of 3.4% in Britain and 15.6% in Brazil [17,19]. Given the relatively low PPV in the British study, along with an estimated 40% sensitivity for preventable ADEs, the Trigger Tool was not adopted in British hospitals.

In Israel, the evidence is scant with estimated ADE rates of 25% and 32% in 1997 and 1998, respectively [20,21]. The objective of the present study was to validate the Trigger Tool in Israel and to define the ADE rates in four different hospitals.

PATIENTS AND METHODS

STUDY POPULATION AND SETTING

The study was a retrospective descriptive correlative analysis surveying four general hospitals in Israel located in different geographical regions. All four hospitals are public academic medical centers varying in size from 326 to 1517 beds. The hospitals had different levels of sophistication in electronic medical chart usage, with one having a full system including CPOE and the other three having a partial system. The study population comprised patients who had been hospitalized in internal medicine and surgical departments between January and December 2014 at each of the four hospitals studied. Inclusion criteria were hospitalized patients 18 years of age or older with a hospital stay between 2 days and 1 month. All hospitalizations that met the inclusion criteria were included. We then randomly selected hospitalizations to be included in the study sample using Microsoft Excel (version 14.0.6212.5000) software (Microsoft Corp, Richmond, CA, USA). The study was approved by the institutional review board at each of the participating hospitals.

CHART REVIEW FOR ADVERSE DRUG EVENTS

ADE identification and characterization was conducted using the methodology as set by the IHI [10]. Prior to the study initiation, all listed researchers reviewed the various ADE triggers and discussed the need for trigger adaptation. Decisions regarding changes were reached only by consensus. Hospitalization charts were initially reviewed by a research nurse to identify triggers and potential ADEs. We reviewed physician orders, medication lists, laboratory reports, admission histories, progress and consultation notes, discharge summaries, and nursing notes. For each record, the total medication dose was manually recorded. Data were abstracted and summarized into electronic forms by trained research nurses. Subsequently, each form was independently reviewed by two physicians (who were the authors of this study). Study personnel underwent training to allow for standardization and optimize reproducibility in data collection. Identified ADEs were further classified by the severity of the ADE and the nature of the condition (e.g., rash, hematologic event, neurologic event). In addition, each event was classified as preventable or non-preventable based on the researcher's clinical judgment. All disagreements in the classification of type, severity, or preventability were resolved by consensus. To prevent potential conflicts of interest, physicians were appointed to review charts that were not from the hospital at which they work.

Apart from looking for trigger-related ADEs, research nurses registered other ADEs identified through chart reviews in an attempt to identify ADEs not captured by the Trigger Tool. Furthermore, in each of the four hospitals, we reviewed the patient safety reporting systems for any ADEs reported by the staff during the study period, specifically those related to the patients included in our study.

SAMPLE SIZE AND STATISTICAL ANALYSIS

Sample size was determined by the Trigger Tool official guidelines. This design required the inclusion of 20 charts per month for the 1 year study. Accordingly, 240 charts were randomly chosen from each hospital, for a total sample size of 960 hospitalizations. Comparison among groups was conducted using ANOVA or chi-square for continuous variables and proportions, respectively.

To validate the research tool, sensitivity was calculated using the ADEs identified by the Trigger Tool and those found by chart reviews. In addition, the PPV of each trigger was calculated by dividing the ADEs actually found with those identified by the triggers in the same cases. Based on previous studies in which low PPV resulted in the withdrawal of the tool, PPV above 10% was required to justify further use of the Trigger Tool [17]. All analyses were two-tailed and $P \leq 0.05$ was considered significant.

RESULTS

Two triggers originally present in the IHI tool were deemed irrelevant to the Israeli healthcare practice and thus were excluded: flumazenil administration (T3) due to updated guidelines for its use and prolonged PTT (T10) due to the limited use of unfractionated heparin in internal medicine and general surgery departments. During the study period, a total of 421 triggers in 279 hospitalizations were identified, of which 75 ADEs among 72 hospitalizations (7.5%, 95% confidence interval [95%CI] 5.8–9.2) were confirmed [Table 1]. The calculated mean PPV was 17.81%, with between-hospital variation of 11.83–24.21% ($P = 0.128$). Two ADEs were identified only by chart review but were not detected by the Trigger Tool (sensitivity of 97%). Compared to patients without ADEs,

patients with an identified ADE were older ($P = 0.009$), were more often females ($P = 0.009$), had higher exposure to daily medication doses ($P < 0.001$), and endured a longer hospital stay ($P < 0.001$) [Table 2].

Overall, 1.54 ADEs were found for every 100 days of hospitalization, 7.8 ADEs per 100 admissions, and 1.81 ADEs for every 1000 doses of medication. Of the 77 ADEs identified, 22.7% were judged as preventable. Fifty events (64.9%) were classified as temporary injury requiring intervention, 25 (32.5%) required prolongation of hospital stay, and 2 (2.6%) events resulted in death [Table 3].

The most common triggers involved prescribing antiemetics (T4, 112 times), abrupt medication stoppage (T18, 100 times), rise in serum creatinine (T15, 57 times), transfer to higher level of care (T19, 37 times), and Kayexalate (sodium polystyrene) administration (T7, 24 times). T4, T18, and T15 were the most frequent triggers that resulted in ADE identification. Further analysis for PPV per individual trigger demonstrated that prescribing antihistamines (T1, 50.0%), leukopenia (T12, 42.86%), hypoglycemia (T8, 41.67%), falls (T16, 38.46%), and vitamin K administration (T2, 36.36%) had the highest predictive values for ADE identification. Triggers for naloxone administration (T5) as well as elevated digoxin levels (T14) were not identified in any of the charts.

Based on trigger frequency and their PPVs, a consensus panel comprised of researchers who were part of this study decided on inclusion and exclusion of triggers, thus suggesting a tool to be used for Israeli hospitals. Compared to the original Trigger Tool, the Israeli customized tool excludes four triggers in total (T3, T5, T10, T14), ending up with 15 triggers.

DISCUSSION

To the best of our knowledge, the current study is the first to measure ADE rates in Israel using a standardized international method that enables the comparison of local ADE rates with other countries. This research is particularly important given the major attention this topic has gained during the last two decades. Varying cultures, policies, economic considerations, and technologies may all affect ADE rates and hence comparisons among countries is somewhat difficult. Nevertheless, in our study ADE rates per 100 admissions were similar to reports in Britain (3.4) and significantly lower than what was reported in Brazil (26.6), the United States (18.7), and Belgium (25.83) [Table 4]. Furthermore, preventable ADE rates are consistent with the previously reported rate of 28% [4].

A mean PPV of 17.8% is higher than the predictive values reported in studies from most other countries (range 4.0%–21.50%). This finding helps to validate the adopted Trigger Tool in Israel. The difference in rates might be due to the trigger adaptation that was designed prior to the initiation of the study initiations. Based on updated guidelines, flumazenil is rarely used

Table 1. Trigger Tool list based on the IHI Trigger Tool, adjusted to Israel

Trigger #	Description	Triggers found	ADEs found	Positive predictive value
T1	Diphenhydramine administration	14	7	50%
T2	Vitamin K administration	11	4	36.36%
T4	Antiemetic administration	112	13	11.61%
T6	Antidiarrheals	8	1	12.5%
T7	Kayexalate (sodium polystyrene) administration	24	4	16.67%
T8	Blood glucose concentration ≤ 50 g/dl	12	5	41.67%
T9	*Clostridium difficile* positive stool	3	0	N/A
T11	INR > 6	1	0	N/A
T12	White blood count ≤ 3000/mm^3	7	3	42.86%
T13	Thrombocytopenia ≤ 50,000/mm^3	9	1	11.11%
T15	Rise in serum creatinine	57	10	17.54%
T16	Over sedation, lethargy, or falls	13	5	38.46%
T17	Rash	13	2	15.38%
T18	Abrupt cessation of medication	100	19	19.0%
T19	Transfer to higher level of care	37	1	2.70%

ADE = adverse drug events, IHI = Institute of Healthcare improvement, INR = international normalized ratio, N/A = not applicable

Table 2. Group characteristics according to the presence of adverse drug events

Variable		No ADE	With ADE	*P* value
Hospitalizations (%)		888 (92.5)	72 (7.5)	–
Age, years		64.0 ± 19.6	70.3 ± 16.1	0.009
Gender, female (%)		430 (48.4)	47 (65.3)	0.009
Department (%)	Surgical	200 (93.9)	13 (6.1)	0.465*
	Medical	688 (92.1)	59 (7.9)	
Mean daily doses		41.4 ± 42.5	63.8 ± 55.3	‹ 0.001
Length of hospital stay, days		4.9 ± 2.8	6.9 ± 4.4	‹ 0.001

*P value for differences in departments relates to differences between ADE rates in surgical and medical departments, significant values are in bold

ADE = adverse drug events

Table 3. List of adverse events severity

Injury level (category)	Number (%)	Preventable (%)	Most prevalent triggers, n (%)
Temporary harm requiring intervention (E)	50 (64.9)	10 (20)	T4: Antiemetic administrations, 13 (26) T18: Abrupt cessation of medication, 11 (22) T1: Antihistamine administration, 7 (14)
Temporary harm requiring prolongation of hospitalization (F)	25 (32.5)	7 (28)	T18: Abrupt cessation of medication, 8 (32) T15: Rise in serum creatinine, 6 (24)
Permanent harm (G)	0 (0)	0 (0)	None
Intervention required to sustain life (H)	0 (0)	0 (0)	None
Death (I)	2 (2.6)	0 (0)	T12: Leukopenia ≤ 3000/mm^3, 1 (50) T13: Thrombocytopenia ≤ 50,000mm^3, 1 (50)

Table 4. Comparison of adverse drug events among countries

	Israel	Britain [17]	Canada [24]	Brazil [19]	Belgium [16]*	USA [8]**	Overall *P* value
Percentage of patients with ADEs§	7.5 (5.8–9.2)	3.4	7.35	15.6 (9.3–34.2)	–	–	–
Number of ADEs per 100 admissions§	8.02 (6.3–9.7)	–	–	26.56 (18.9–34.2)	25.83 (20.3–31.4)	18.7 (16.1–21.5)	‹ 0.001
Positive predictive value (%)	17.8	4.0	–	14.35	21.50	–	0.15***
Preventable ADE (%)	22.07	1.0	–	–	34.9	37.4	0.053***
Israel vs. other countries Number of ADEs per 100 admissions	–	N/A	N/A	‹ 0.001	‹ 0.001	‹ 0.001	–

*Including ADEs developing prior to admission
**Prevalence using Trigger tool only
***Comparison excluding Britain
§95% confidence interval
ADE = adverse drug events, N/A = not applicable

for benzodiazepine overdose and PTT monitoring is irrelevant given the rarity of unfractionated heparin use in internal medicine and general surgery departments; therefore, both triggers were excluded. Furthermore, the use of electronic patient charts with computerized systems with alerts in cases of potential DDIs might have also contributed to the low observed rates.

Not surprisingly, patients in the current study who underwent an ADE were older and received more medication doses per day. These observations are consistent with previous studies demonstrating similar associations with particular attention to polypharmacy as a risk factor for adverse events [1]. Multiple dose regimens expose hospitalized patients to more encounters in which a potential mistake can take place and hence, simple daily regimens might further reduce ADE rates. Similar to previous studies, our study also demonstrated an association between ADE rates and longer hospital stay [19,22]. This consequence is another part of the additional costs associated with adverse events, which are estimated to be as high as US$3511 for preventable ADEs [5], and emphasizes the many ways in which improving patient safety can contribute to hospitals and healthcare systems [23].

The importance of this study in providing the validated Trigger Tool for use in Israel is in the ability to compare different hospitals within Israel as well as across other countries, over different periods of times, and with a standardized method. This research design incorporated quality control and patient safety, together with other well-recognized measures (e.g., acquired infections). However, the Trigger Tool screening method may not be applicable on a continuous basis in all hospitals due to the resources needed, but rather can be implemented as a periodic in-depth survey by official regulators. Noteworthy is the information technology development and its involvement in every aspect of the daily professional routine, which calls for an automated method to monitor ADEs [24].

The present study has several limitations. The use of the Trigger Tool to identify ADE is limited since it does not capture all ADEs. Nevertheless, we attempted to identify ADEs not recognized through the tool itself by using full chart reviews and archives of patient safety reporting. Thus, we believe that the high sensitivity (97%) provides a good enough estimation. Noteworthy is also the difference in the level of electronic medical records at the four hospitals. These differences could have an impact on the actual ability to detect ADEs. However, the Trigger Tool is reported to work well with electronic records. [8,25]

CONCLUSIONS

ADEs rates measured in four hospitals in Israel are similar to those described in the international literature. This, together with the high PPV demonstrated, further supports the validity of the Trigger Tool in Israel as a standardized method. Further studies should evaluate the between-hospital and regional differences in ADE rate, in particular for preventable events. This research may help in our understanding of how different methods are used to prevent ADEs, such as computerized decision support or pharmacist-led initiatives. Success in reducing ADEs could impact future local as well as national policy.

Acknowledgements

This study was supported by the Israel National Institute for Health Policy Research

The authors thank the following collaborators Ms. Ortal Sharlin, Dr. Merav Ben-Natan, Ms. Hadassa Rosenblat, Ms. Tamar Wechter, Ms. Orly Statskovits, Ms. Julia Bartal, Ms. Orly Haccoun and Ms. Natalia Sheplevich

Correspondence

Dr. E. Zimlichman
Management, Sheba Medical Center, Tel Hashomer 5265601, Israel
Phone: (972-3) 530-7267
Fax: (972-3) 530-7071
email: eyal.zimlichman@sheba.health.gov.il

References

1. Zhou L, Rupa AP. Categorization and association analysis of risk factors for adverse drug events. *Eur J Clin Pharmacol* 2017; 74 (4): 389-404.
2. Aspden P, Wolcott JA, Bootman JL, et al. Committee on Identifying and Preventing Medication Errors. *Preventing medication errors: quality chasm series.*

Washington (DC): The National Academies Press; 2006. [Available from https://doi.org/10.17226/11623]. [Accessed 20 May 2018].

3. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 1991; 324 (6): 377-84.
4. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA* 1995; 274 (1): 29-34.
5. Hug BL, Keohane C, Seger DL, Yoon C, Bates DW. The costs of adverse drug events in community hospitals. *Jt Comm J Qual Patient Saf* 2012; 38 (3): 120-6.
6. Institute of Medicine (US) Committee on Quality of Health Care in America. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington (DC): National Academies Press (US); 2001.
7. Connelly TP, Korvek SJ. Computer Provider Order Entry (CPOE). StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2017 Jun–2017 Nov 8. [Available from https://www.ncbi.nlm.nih.gov/books/NBK470273/]. [Accessed 1 June 2018].
8. Leung AA, Keohane C, Amato M, et al. Impact of vendor computerized physician order entry in community hospitals. *J Gen Intern Med* 2012; 27 (7): 801-7.
9. Jha AK, Kuperman GJ, Teich JM, et al. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *J Am Med Inform Assoc* 1998; 5 (3): 305-14.
10. Institute of Healthcare Improvement. Trigger Tool for measuring adverse drug events. 2004. [Available from http://www.ini.org/resrources/pages/tools/triggertoolformeasuringadversedrugevents.aspx]. [Accessed 8 Aug 2014].
11. De Almeida SM, Romulado A, de Abreu Ferraresi A, Zelezoglo GR, Marra AR, Edmond MB. Use of a trigger tool to detect drug reactions in an emergency department. *BMC Pharmacol Toxicol* 2017; 18 (1): 71.
12. Deilkas ET, Risberg MB, Haugen M, et al. Exploring similarities and differences in hospital adverse events rates between Norway and Sweden using Global Trigger Tool. *BMJ Open* 2017; 7 (3): e012492.
13. Rutberg H, Borgstedt-Risberg M, Gustafson P, Unbeck M. Adverse events in orthopedic care identified via the Global Trigger Tool in Sweden – implications on preventable prolonged hospitalizations. *Patient Saf Surg* 2016; 12: 23.
14. Mortaro A, Moretti F, Pascu D, et al. Adverse events detection through Global Trigger Tool methodology: results from a 5-year study in an Italian Hospital and opportunities to improve interrater reliability. *J Patient Saf* 2017. [Epub ahead of print].
15. Karpov A, Parcero C, Mok CP, et al. Performance of trigger tools in identifying adverse drug events in emergency patients: a validation study. *Br J Clin Pharmacol* 2016; 82 (4): 1048-57.
16. Carnevali L, Krug B, Amant F, et al. Performance of the adverse drug event Trigger Tool and the global Trigger Tool for identifying adverse drug events: experience in a Belgian hospital. *Ann Pharmacother* 2013; 47 (11): 1414-9.
17. Franklin BD, Birch S Schachter, Barber N. Testing a trigger tool as a method of detecting harm from medication errors in a UK hospital: a pilot study. *Int J Pharm Pract* 2010; 18: 305-11.
18. Perez Zapata Al, Gutierrez Samaniego M, Rodriguez Cuellar E, Andres Esteban EM, Gomez de la Camara A, Ruiz Lopez P. Detection of adverse events in general surgery using the "Trigger Tool" methodology. *Cir Esp* 2015; 93 (2): 84-90.
19. Rozenfled S, Giordani F, Coelho S. Adverse drug events in hospital: pilot study with Trigger Tool. *Rev Sauide Publica* 2013; 47: 1102-11.
20. Azaz-Livshits T, Levy M, Sadan B, Shalit M, Geisslinger G, Brune K. Computerized surveillance of adverse drug reactions in hospital: pilot study. *Br J Clin Pharmacol* 1998; 45 (3): 309-14.
21. Levy M, Azaz-Livshits T, Sadan B, Shalit M, Geisslinger G, Brune K. Computerized surveillance of adverse drug reactions in hospital: implementation. *Eur J Clin Pharmacol* 1999; 54 (11): 887-92.
22. Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. Adverse drug events prevention study group. *JAMA* 1997; 277: 307-11.
23. Zimlichman E, Keohane C, Franz C, et al. Return on investment for vendor computerized physician order entry in four community hospitals: the importance of decision support. *Jt Comm J Qual Patient Saf* 2013; 39 (7): 312-8.
24. Lau I, Kirkwood A. Measuring adverse drug events on hospital medicine units with the Institute for Healthcare Improvement Trigger Tool: a chart review. *Can J hosp Pharm* 2014; 67 (6): 423-8.
25. Hug BL, Witkowski DJ, Sox CM, et al. Adverse drug event rates in six community hospitals and the potential impact of computerized physician order entry for prevention. *J Gen Intern Med* 2009; 25: 31-8.

Capsule

Deconstructing probiotics

Besides supporting host metabolism, our intestinal microbiota also plays a vital role in modulating functions of immune cells in the gut. **Verma** and colleagues examined how a particular probiotic strain, *Bifidobacterium bifidum*, promotes the generation of regulatory T cells (T_{regs}) in the intestine. β-glucan/galactan polysaccharides derived from the cell wall of *B. bifidum* were responsible for promoting T_{reg} induction in the intestine. This process was dependent on intestinal dendritic cells that express Toll-like receptor 2. Thus, microbial components, rather than live microbes, could potentially be used to treat microbial dysbiosis associated with gastrointestinal disorders, including colitis and Crohn's disease.

Sci Immunol 2018; 3: eaat6975

Eitan Israeli

Capsule

Cancer chromatin accessibility landscape

The Cancer Genome Atlas (TCGA) provides a high-quality resource of molecular data on a large variety of human cancers. **Corces** and co-authors used a recently modified assay to profile chromatin accessibility to determine the accessible chromatin landscape in 410 TCGA samples from 23 cancer types. When the data were integrated with other omics data available for the same tumor samples, inherited risk loci for cancer predisposition were revealed, transcription factors and enhancers driving molecular subtypes of cancer with patient survival differences were identified, and non-coding mutations associated with clinical prognosis were discovered.

Science 2018; 362: eaav1898

Eitan Israeli